Web audio at CurrentPsychiatry.com
Dr Riba: Choosing treatments for depressed breast cancer patients

ONLINE ONLY

Current PSYCHIATRY

Tailoring depression treatment for women with breast cancer

Factors unique to these patients help determine treatment strategies

© CORBIS/VICKY EMPTAGE

Prachi Agarwala, MD
Psychiatry Resident, PGY-V

Michelle B. Riba, MD, MS
Clinical Professor

• • • •

Department of Psychiatry
University of Michigan
Ann Arbor, MI

Psychological distress among patients with breast cancer is common and is linked to worse clinical outcomes. Depressive and anxiety symptoms affect up to 40% of breast cancer patients,[1] and depression is associated with a higher relative risk of mortality in individuals with breast cancer.[2] Psychotropic medications and psychotherapy used to treat depression in patients without carcinoma also are appropriate and effective for breast cancer patients. However, some patients present distinct challenges to standard treatment. For example, growing evidence suggests that some selective serotonin reuptake inhibitors (SSRIs) may reduce the effectiveness of tamoxifen, a chemotherapeutic agent. This article discusses challenges in diagnosing and treating depression in breast cancer patients and reviews evidence supporting appropriate psychiatric care.

Increased vulnerability

In 10% to 30% of women, a breast cancer diagnosis may lead to increased vulnerability to depressive disorders, including adjustment disorders with depressed mood, major depressive disorder (MDD), and mood disorders related to general medical conditions.[3,4] The risk of developing a depressive disorder is highest in the year after receiving the breast cancer diagnosis.[4]

A woman's risk of developing a depressive disorder may depend on the type of cancer treatment she receives. For example, breast asymmetry is common after breast conserving surgery. Waljee et al[5] found that wom-

Depression and breast cancer

Clinical Point

Somatic symptoms of depression may be mistaken for side effects of breast cancer treatment

ONLINE ONLY

Discuss this article at http://CurrentPsychiatry.blogspot.com

Table 1

Risk factors for psychiatric distress related to breast cancer

Past psychiatric illness
Family history of psychiatric illness
Younger age (<45 years)
Having young children
Limited social support
Substance use
Single status
Pain
Physical disability
Poor family coherence
Financial strain

Source: Adapted from reference 10

en with breast asymmetry had increased fears of cancer recurrence and more feelings of self-consciousness. More pronounced asymmetry led to a higher incidence of depressive symptoms. However, among 90 patients undergoing bilateral prophylactic mastectomy, the rate of depression had not changed 1 year after the procedure.[6] Chemotherapy, particularly at high doses, is a risk factor for depression.[4,7,8]

Self-blame for developing breast cancer can affect mood. In 2007, Friedman et al[9] determined that higher levels of self-blame correlated with higher levels of depression and decreased quality of life. Women often blamed themselves for various reasons, including:

- poor coping skills
- anxiety about their health and treatments
- inability to express emotions
- delays in medical consultation.

Exacerbated symptoms and side effects. Women with depression often experience increased side effects from cancer treatments, and the subjective experience of these effects—including hot flashes, cognitive impairment, pain, and sexual dysfunction—likely is intensified.[4] Somatic symptoms of depression may be exacerbated by cancer treatment side effects or mistaken for effects of the treatment. When somatic symptoms of depression are mistaken for treatment side effects, depression—and the opportunity to treat it—can be overlooked.[10]

Depression may be a risk factor for poor adherence to cancer treatment. In a quantitative review of studies correlating depression and medical treatment noncompliance, DiMatteo et al[11] determined that compared with nondepressed patients, those with depression were 3 times more likely to not adhere to treatment recommendations; this review was not limited to cancer patients. Depressive symptoms—notably poor concentration and amotivation—can create the impression that a patient is poorly adherent. Women with comorbid depression and breast cancer may have difficulty understanding treatment recommendations or remembering daily treatment goals.[4]

Appropriate screening tools

Factors that may increase a breast cancer patient's risk for developing a psychiatric disorder are listed in ***Table 1***.[10] Many depression screening tools are available; below we describe 3 commonly used for patients with breast cancer.

The National Comprehensive Cancer Center Distress Thermometer allows patients to rate their overall distress level over the past week on a scale from 0 to 10, using a visual analogue.[12] The Distress Thermometer has been validated for several cancer populations and in different parts of the world. A score of 7 has both good sensitivity and specificity for detecting depression in breast cancer patients. Consider a complete psychiatric evaluation for patients with scores ≥7.[13]

The Profile of Mood States questionnaire[14] is a reliable, valid 65-item questionnaire often used in studies of mood dysregulation and breast cancer. Subscales include depression-dejection, tension-anxiety, anger-hostility, confusion-bewilderment, vigor-activity, and fatigue-inertia. Using a 5-point Likert scale, patients rate their symptoms over the past week. Subscale scores are then added to a total mood disturbance score.[14,15]

The Hospital Anxiety and Depression Scale (HADS) is a sensitive, reliable 14-

continued on page 45

continued from page 40

item scale that is commonly used to study depression and anxiety in patients with breast cancer.[16] HADS includes two 7-item subscales—anxiety and depression—and answers are scored on a 4-point Likert scale. Patients are asked to respond quickly and avoid thinking too long about their answers.

Psychotherapeutic options

Behavioral therapies can diminish symptoms of depression, according to a review of studies and practice guidelines on managing depression in cancer patients.[17] Group interventions, in particular, can be valuable. Anderson et al[18] found that group cohesion, member connectedness, and more sessions correlated with decreased psychological distress.

Psychoeducation aims to provide medical information and discuss cancer's causes, prognosis, and treatment strategies. Group settings can help improve communication and problem-solving skills. In a randomized controlled trial (RCT) of 203 women with breast cancer, psychoeducational group treatment reduced depression, anger, and fatigue.[19]

Cognitive-behavioral therapy (CBT) helps patients identify and restructure negative thoughts and increase positive, adaptive behaviors. Hunter et al[20] noted significant improvement in depressed mood, anxiety, and sleep in 17 women experiencing menopausal symptoms who received group CBT after completing breast cancer treatment. In 1 study, 124 patients with metastatic breast cancer who received 8 weekly sessions of group CBT reported reduced depression and mood disturbance and improved self-esteem compared with a no-therapy control group.[21]

Supportive-expressive therapy (SET) is a manual-based therapy that focuses on increasing social support, improving symptom control, and enhancing communication between the patient and treatment team. Affective expression helps lead the therapist to issues that should be addressed. Evidence on the effectiveness of SET for patients with breast cancer is mixed. A study of 357 women with breast cancer who were randomly assigned to 12-week group SET or an educational control condition found no evidence that SET reduced distress.[22] However, a trial of 485 women with advanced breast cancer who were randomly assigned to group SET plus relaxation therapy or relaxation therapy alone showed that SET improved quality of life, including protection against depression.[23]

Mindfulness-based stress reduction (MBSR) is a standardized form of meditation and yoga. Clinicians teach patients visualization, breathing exercises, and meditation to help them become aware of the body's reaction to stress and how to regulate it. In an RCT of 84 female breast cancer survivors, a 6-week MBSR program diminished depressive symptoms, improved physical functioning, and reduced fear of cancer recurrence.[24]

Evidence for antidepressants

SSRIs. Expert consensus guidelines on treating depression in women recommend an SSRI as a first-line agent.[25] In RCTs, fluoxetine, paroxetine, and sertraline were more effective than placebo in treating depression and related symptoms specifically in women with breast cancer ***(Table 2, page 46)***.[26-28]

The interaction between SSRIs and chemotherapy agents is a concern. Tamoxifen decreases the rate of death from breast cancer in hormone receptor positive breast cancers.[29] Endoxifen, a potent anti-estrogen, is an active metabolite of tamoxifen via cytochrome P450 (CYP) 2D6. Goetz et al[30] demonstrated that women with decreased or inhibited metabolism via CYP2D6 had significantly shorter times to breast cancer recurrence, compared with women with extensive CYP2D6 metabolism.

SSRIs can varyingly inhibit CYP2D6. In a prospective trial of 158 breast cancer patients receiving tamoxifen, paroxetine and fluoxetine were found to be strong inhibitors of CYP2D6 and led to low levels of endoxifen.[31] In contrast, weaker inhibi-

Clinical Point

Depressive symptoms can create the impression that a patient is poorly adherent to cancer treatments

Depression and breast cancer

Clinical Point

Patients who receive tamoxifen should be treated with an antidepressant with minimal effect on CYP2D6 metabolism

Table 2

Evidence supporting SSRI use in patients with breast cancer*

Study	Design	Results
Navari et al, 2008[26]	193 patients with newly diagnosed early-stage breast cancer were randomized to fluoxetine, 20 mg/d, or placebo for 6 months	Fluoxetine reduced depressive symptoms, improved quality of life, and led to higher completion of adjuvant chemotherapy and/or hormone therapy
Roscoe et al, 2005[27]	94 women with breast cancer receiving at least 4 cycles of chemotherapy were randomized to paroxetine, 20 mg/d, or placebo	Paroxetine significantly reduced depression during chemotherapy
Kimick et al, 2006[28]	62 women with early-stage breast cancer receiving the chemotherapy agent tamoxifen who reported hot flashes were randomized to sertraline, 50 mg/d, or placebo for 6 weeks	Sertraline was significantly more effective than placebo at reducing hot flashes

*Breast cancer patients who receive tamoxifen generally should be treated with an antidepressant that has minimal effect on cytochrome P450 2D6 metabolism, such as citalopram, escitalopram, venlafaxine, or desvenlafaxine

SSRIs: selective serotonin reuptake inhibitors

tors, including sertraline and citalopram, led to intermediate levels of endoxifen. In a retrospective cohort study, Kelly et al[32] demonstrated that women treated with paroxetine, in combination with tamoxifen, had an increased risk of death compared with women treated with other SSRIs or venlafaxine and tamoxifen. They estimated that paroxetine use in women treated with tamoxifen would lead to 1 additional breast cancer death per 20 women within 5 years of discontinuing tamoxifen.

According to American Psychiatric Association practice guidelines for treatment of MDD, depressed breast cancer patients who receive tamoxifen generally should be treated with an antidepressant that has minimal effect on CYP2D6 metabolism, such as citalopram, escitalopram, venlafaxine, or desvenlafaxine.[33]

Serotonin-norepinephrine reuptake inhibitors (SNRIs) may be used to treat depressive disorders. In addition, venlafaxine may be helpful in treating post-mastectomy pain syndrome. Approximately one-half of patients who undergo mastectomy or breast reconstruction may experience a postoperative pain syndrome.[34] The most common symptom is a burning, stabbing pain in the axilla, arm, and chest wall of the affected side. This pain is worsened by movement and is poorly responsive to opioids.[35]

In a 10-week RCT of 13 patients with neuropathic pain after breast cancer treatment, venlafaxine significantly improved pain relief compared with placebo, although the drug did not affect depression or anxiety.[36] In a study of 100 patients given venlafaxine or placebo for 2 weeks starting the night before undergoing partial or radical mastectomy with axillary dissection, those receiving venlafaxine had a significantly lower incidence of pain in the chest wall, arm, and axillary region, and scores of pain with movement were decreased.[37] There was no difference in opioid usage between groups.

Tricyclic antidepressants have been demonstrated to be effective in breast cancer patients. Side effects—notably anticholinergic effects—limit their use as antidepressants, especially when compared with SSRI treatment. In a study that randomly assigned 179 women with breast cancer to paroxetine, 20 to 40 mg/d, or amitriptyline, 75 to 150 mg/d, anticholinergic effects were almost twice as frequent in the amitriptyline group (19%) compared with paroxetine (11%).[38] In a 4-week double-blind, placebo-controlled crossover trial of 15 breast cancer patients, amitriptyline significantly relieved neuropathic pain, but its adverse effects made most patients unwilling to use the medication regularly.[39]

continued on page 48

continued from page 46

Depression and breast cancer

Clinical Point

Venlafaxine may be helpful in treating post-mastectomy pain syndrome

Related Resources

- American Cancer Society. www.cancer.org.
- National Comprehensive Cancer Network. www.nccn.org.

Drug Brand Names

Amitripyline • Elavil
Citalopram • Celexa
Desvenlafaxine • Pristiq
Escitalopram • Lexapro
Fluoxetine • Prozac
Paroxetine • Paxil
Sertraline • Zoloft
Tamoxifen • Nolvadex
Venlafaxine • Effexor

Disclosure

The authors report no financial relationship with any company whose products are mentioned in this article or with manufacturers of competing products.

References

1. Von Ah D, Kang DH. Correlates of mood disturbance in women with breast cancer: patterns over time. J Adv Nurs. 2008;61(6):676-689.
2. Hjerl K, Andersen EW, Keiding N, et al. Depression as a prognostic factor for breast cancer mortality. Psychosomatics. 2003;44:24-30.
3. Stanton AL. Psychosocial concerns and interventions for cancer survivors. J Clin Oncol. 2006;24(32):5132-5137.
4. Fann JR, Thomas-Rich AM, Katon WJ, et al. Major depression after breast cancer: a review of epidemiology and treatment. Gen Hosp Psychiatry. 2008;30:112-126.
5. Waljee JF, Hu ES, Ubel PA, et al. Effect of esthetic outcome after breast-conserving surgery on psychosocial functioning and quality of life. J Clin Oncol. 2008;26(20):3331-3337.
6. Brandberg Y, Sandelin K, Erikson S, et al. Psychological reactions, quality of life, and body image after bilateral prophylactic mastectomy in women at high risk for breast cancer: a prospective 1-year follow-up study. J Clin Oncol. 2008;26(24):3943-3949.
7. Lee KC, Ray T, Hunkeler E, et al. Tamoxifen treatment and new onset depression in breast cancer patients. Psychosomatics. 2007;48:205-210.
8. Thornton LM, Carson WE, Shapiro CL, et al. Delayed emotional recovery after taxane-based chemotherapy. Cancer. 2008;113(3):638-647.
9. Friedman LC, Romero C, Elledge R, et al. Attribution of blame, self-forgiving attitude and psychological adjustment in women with breast cancer. J Behav Med. 2007;30:351-357.
10. Spiegel D, Riba M. Psychological aspects of cancer. In: DeVita VT, Lawrence TS, Rosenberg SA, eds. Principles and practice of oncology. 8th ed. Philadelphia, PA: Lippincott Williams & Wilkins; 2008:2817-2826.
11. DiMatteo MR, Lepper HS, Croghan TW. Depression is a risk factor for noncompliance with medical treatment. Arch Intern Med. 2000;160:2101-2107.
12. National Comprehensive Cancer Network. Practice guidelines in oncology—distress management v.1.2010. 2010. Available at: http://www.nccn.org. Accessed October 5, 2010.
13. Hegel MT, Collins ED, Kearing S. Sensitivity and specificity of the distress thermometer for depression in newly diagnosed breast cancer patients. Psychooncology. 2008; 17:556-560.
14. Lorr M, McNair DM, Droppleman LF. POMS profile of mood states. Available at: http://www.mhs.com/product.aspx?gr=cli&prod=poms&id=overview. Accessed September 29, 2010.
15. Classen C, Butler LD, Koopman C. Supportive-expressive group therapy and distress in patients with metastatic breast cancer: a randomized clinical intervention trial. Arch Gen Psychiatry. 2001;58:494-501.
16. Zigmond AS, Snaith RP. The hospital anxiety and depression scale. Acta Psychiatr Scand. 1983;67:361-370.
17. Barsevick AM, Sweeney C, Haney E, et al. A systematic qualitative analysis of psychoeducational interventions for depression in patients with cancer. Oncol Nurs Forum. 2002;29(1):73-84.
18. Andersen BL, Shelby RA, Golden-Kreutz DM. RCT of a psychological intervention for patients with cancer: I. Mechanisms of change. J Consult Clin Psychol. 2007; 75(6):927-938.
19. Dolbreault S, Cayrou S, Bredart A, et al. The effectiveness of a psycho-educational group after early-stage breast cancer treatment: results of a randomized French study. Psychooncology. 2009;18:647-656.
20. Hunter MS, Coventry S, Hamed H, et al. Evaluation of a group cognitive behavioural intervention for women suffering from menopausal symptoms following breast cancer treatment. Psychooncology. 2009;18(5):560-563.
21. Edelman S, Bell DR, Kidman AD. A group cognitive behaviour therapy programme with metastatic breast cancer patients. Psychooncology. 1999;8(4):295-305.
22. Classen CC, Kraemer HC, Blasey C, et al. Supportive-expressive group therapy for primary breast cancer patients: a randomized prospective multicenter trial. Psychooncology. 2008;17:438-447.
23. Kissane DW, Grabsch B, Clarke DM, et al. Supportive-expressive group therapy for women with metastatic

Bottom Line

Women are at risk for depression in all stages of breast cancer. Several forms of psychotherapy can be effective for these patients. Although pharmacotherapy for depression generally is the same for breast cancer patients as for those without carcinoma, be vigilant for factors that influence treatment strategies, such as the possible effect of SSRIs on CYP2D6 metabolism in patients receiving tamoxifen.

breast cancer: survival and psychosocial outcome from a randomized control trial. Psychooncology. 2007;16(4):277-286.
24. Lengacher CA, Johnson-Mallard V, Post-White J, et al. Randomized controlled trial of mindfulness-based stress reduction (MBSR) for survivors of breast cancer. Psychooncology. 2009;18:1261-1272.
25. Altshuler LL, Cohen LS, Moline ML, et al. Treatment of depression in women: a summary of expert consensus guidelines. J Psychiatr Pract. 2001;7(3):185-208.
26. Navari RM, Brenner MC, Wilson MN. Treatment of depressive symptoms in patients with early stage breast cancer undergoing adjuvant therapy. Breast Cancer Res Treat. 2008;112(1):197-201.
27. Roscoe JA, Morrow GR, Hickok JT, et al. Effect of paroxetine hydrochloride on fatigue and depression in breast cancer patients receiving chemotherapy. Breast Cancer Res Treat. 2005;89(3):243-249.
28. Kimmick GG, Lovato J, McQuellon R, et al. Randomized, double-blind, placebo-controlled crossover study of sertraline (Zoloft) for treatment of hot flashes in women with early stage breast cancer taking tamoxifen. Breast J. 2006;12(2):114-122.
29. Early Breast Cancer Trialists' Collaborative Group (EBCTCG). Effects of chemotherapy and hormonal therapy for early breast cancer on recurrence and 15-year survival: an overview of the randomized trials. Lancet. 2005; 365(9472):1687-1717.
30. Goetz MP, Knox SK, Suman VJ, et al. The impact of cytochrome P450 2D6 metabolism in women receiving adjuvant tamoxifen. Breast Cancer Res Treat. 2007; 101(1):113-121.
31. Borges S, Desta Z, Li L, et al. Quantitative effect of CYP2D6 genotype and inhibitors on tamoxifen metabolism: implication for optimization of breast cancer treatment. Clin Pharmacol Ther. 2006;80(1):61-74.
32. Kelly CM, Juurlink DN, Gomes T, et al. Selective serotonin reuptake inhibitors and breast cancer mortality in women receiving tamoxifen: a population based cohort study. BMJ. 2010;8:340;c693.
33. Gelenberg AJ, Freeman MP, Markowitz JC, et al. Practice guideline for the treatment of patients with major depressive disorder. 3rd ed. Arlington, VA: American Psychiatric Publishing, Inc. 2010.
34. Vadivelu N, Schreck M, Lopez J, et al. Pain after mastectomy and breast reconstruction. Am Surg. 2008;74(4):285-296.
35. Stevens PE, Dibble SL, Miaskowski C. Prevalence, characteristics and impact of post-mastectomy pain syndrome: an investigation of women's experiences. Pain. 1995;61:61-68.
36. Tasmuth T, Hartel B, Kalso ET. Venlafaxine in neuropathic pain following treatment of breast cancer. Eur J Pain. 2002;6:17-24.
37. Reuben SS, Makari-Judson G, Lurie SD. Evaluation of efficacy of the perioperative administration of venlafaxine XR in the prevention of post-mastectomy pain syndrome. J Pain Sympt Manage. 2004;27(2):133-139.
38. Pezzella G, Moslinger-Gehmayr R, Contu A. Treatment of depression in patients with breast cancer: a comparison between paroxetine and amitriptyline. Breast Cancer Res Treat. 2001;70(1):1-10.
39. Kalso ET, Tasmuth T, Neuvonen PJ. Amitriptyline effectively relieves neuropathic pain following treatment of breast cancer. Pain. 1996;64:293-302.

Clinical Point

Tricyclics can be effective in breast cancer patients but anticholinergic effects limit their use