

Breast cancer and depression: issues in clinical care

Thingbaijam B. Singh,¹ Laishram J. Singh,² Bhushan B. Mhetre¹

¹ Department of Psychiatry, Regional Institute of Medical Sciences, Imphal, India

² Department of Radiotherapy, Regional Institute of Medical Sciences, Imphal, India

Abstrak

Pasien dengan kanker payudara banyak yang mengalami gangguan dan hampir seluruhnya mengalami depresi yang dapat memperberat gejala fisik, meningkatkan gangguan fungsional, dan membuat kepatuhan berobat menjadi rendah. Kami melakukan tinjauan pustaka yang tersedia di PubMed tentang prevalensi, besar gangguan, kemampuan coping, dan metode penatalaksanaan depresi berat pada wanita dengan kanker payudara dari tahun 1978 sampai 2010. Diagnosis dan penatalaksanaan episode depresi pada wanita dengan kanker payudara merupakan tantangan karena gejala yang tumpang tindih dan kondisi penyerta. Depresi berat sering disepelekan dan penatalaksanaan tidak adekuat pada pasien kanker payudara. Tinjauan ini menekankan pada masalah dalam identifikasi dan pengelolaan depresi pada pasien kanker payudara dengan latar klinis. (*Med J Indones.* 2012;21:240-6)

Abstract

Many of breast-cancer patients experience distress and most of them experience depression which may lead to amplification of physical symptoms, increased functional impairment, and poor treatment adherence. We did a review on available literature from PubMed about prevalence, distress magnitudes, coping styles, and treatment methods of major depression in women with breast cancer from 1978 to 2010. Diagnosis and treatment of depressive episodes in women with breast cancer is challenging because of overlapping symptoms and co-morbid conditions. Major depression is often under-recognized and undertreated among breast cancer patients. This review highlighted the issues on identifying and managing depression in breast cancer patients in clinical settings. (*Med J Indones.* 2012;21:240-6)

Keywords: Breast cancer; coping; depression; distress

Nowadays, breast cancer is one of the most common malignancies and the leading cause of cancer mortality in women in developed and developing countries.¹ The diagnosis of breast cancer should not only include physical condition but also social and psychological condition. This is due to the importance of breast in the women's body image, sexuality and motherhood. The 5-year survival rates of patients with breast cancer have increased to the extent of 89%.¹ The important concern today is to improve the quality of life (QoL) among survivors. Survivors of breast cancer often experience aversive symptoms like fatigue, cognitive problems, and menopausal symptoms. Psychological distress among patients with breast cancer is linked with a worse clinical outcome and at the same time advanced stages of cancer seem to be most stressful and have higher risk for emotional distress.

Prevalence of major depression increases with cancer progression, from 11% associated with early-stage, node-negative breast cancer to as great as 50% in women with metastatic breast cancer undergoing palliative therapies.² Psychological distress due to anxiety and depression are known to predict subsequent quality of life or overall survival in breast cancer patients even years after the disease diagnosis and treatment.³

The psychological response to the diagnosis of breast cancer varies considerably among women.

These variations may be due to differences in coping strategies, personality profiles, and available social supports, and to an extent of consultation skills with her medical providers, especially the surgeon who does the breaking of the bad news.⁴ Most women undergo concerns and fears about physical appearance and disfigurement, moreover the uncertainty regarding recurrence and fear of death. Among sexually active women, significant body-image-problems are associated with mastectomy, hair loss from chemotherapy, weight gain or loss, and the difficulty of partners in understanding her feelings.⁵ In 10-30% of women, the diagnosis of breast cancer may lead to increase vulnerability to depressive disorders which include adjustment disorders with depressed mood, major depressive disorder, and mood disorders related to the general medical condition.⁶ The risk of developing a depressive disorder is highest in the year after receiving diagnosis of breast cancer⁷ (Table 1).

There is more psychological distress in young women than older women. Older patients appear to cope better and this may be due to their prior exposure to the current threats leading to development of appropriate coping mechanisms. Additional concerns, especially to the young women include hair loss induced by chemotherapy, weight gain, and abrupt onset of menopausal symptoms, as well as decreased sexual

Table 1. Associated factors of psychological distress in breast cancer

▪ Past psychiatric illness	▪ Family history of psychiatric illness
▪ Younger age (< 45 years)	▪ Having young children
▪ Breast asymmetry	▪ Associated menopausal symptoms
▪ Pain	▪ Physical disability
▪ Adverse effects of chemotherapy	▪ Co-morbid substance use
▪ Poor coping and mental adjustment	▪ Self blame
▪ Limited social support	▪ Single status
▪ Poor family coherence	▪ Financial strain

Adapted from: Spiegel D, Riba M. Psychological aspects of cancer. In: Devita VT, Lawrence TS, Rosenberg SA, editors. Principles and practise of oncology. 8th ed. Philadelphia, PA: Lippincott Williams and Wilkins; 2008.

desire and vaginal dryness resulted by hormonal therapy. Moreover, they also feel fears for the future of their children and anxiety about the future ability to conceive and raise their children.⁸

Risk for women to develop a depressive disorder does not only depends on the stage of breast cancer, but also the type of cancer treatment received. Women with breast asymmetry after surgical treatment had increased fear of cancer recurrence and feelings of self-consciousness.⁹ Chemotherapy, particularly at high doses is a separate factor for depression in patients with breast cancer.^{10,11}

Self-blaming and coping

Coping efforts involve a person's perceived adjustment to illness when confronting distressing symptoms referring to psychological, physiological, social, and existential response to illness.¹² Self-blame because of breast cancer may affect mood. They blame themselves for various reasons including treatment delays, poor coping skill, and also limited awareness about their health.¹³

A study of newly diagnosed breast cancer patients showed the scoring > 5 of distress thermometer was most commonly reported due to "emotional causes" related to the disease itself, followed with distress related to uncertainty in treatment, physical symptoms, practical life problems, family problems, and spiritual crises.¹⁴ Thus, nature of problems faced after knowing the diagnosis of cancer is determinant of coping dimensions. Mental adjustments to cancer diagnosis can be discussed in various dimensions of coping styles. Factors like compliance of medical therapy, information of the disease, and social support influence coping strategies.¹⁵ Acceptance and positive reframing of altered body image improve self-esteem and reduce psychological morbidity like depression.¹⁶

Depressive symptoms, breast cancer, and cancer treatment

Depressive symptoms can be emotional e.g.: feeling sad, hopelessness, suicidal thought; and physical e.g.: vague bodily pains, lack of energy, loss of sleep, loss of appetite. Depression with predominant in physical symptoms is called depression with somatoform symptoms. The disease itself and breast cancer treatment interact with expression of both emotional and physical symptoms of depression. Depressive symptoms also modify the symptoms related to breast cancer and treatment side effects.

Subjective side effects of cancer treatment is intensified if depression co-exists with breast cancer.¹¹ Also somatic symptoms of depression may be mistakenly considered as side effects of the treatment.¹⁷ Depressed patients are more likely not to adhere to the recommended treatment because of desperation or forgetfulness in treatment associated. Understanding recommended treatment and remembering daily treatments' goals are challenging task for cancer patients with co-morbid depression.¹¹

Depressive symptoms are exacerbated by ongoing cancer treatment, either by side effects of anti-neoplastic drugs or direct effect of those drugs on CNS neurotransmitters. Repeated administration of chemotherapy results in progressively worse and more enduring impairments in sleep-wake activity rhythms.¹⁸ Moreover, the anti-estrogenic effects of tamoxifen at postsynaptic receptors have been found to contribute to depressive symptoms.¹⁹

Depression, immune response, and cancer

Chronic stress and depression give rise to persistent activation of the hypothalamic-pituitary-adrenal and sympathetic-adrenal-medullary axis which will impair immune response and contribute in the development and progression of certain types of cancer. Behavioral

strategies, psychological, and psycho-pharmacological interventions that enhance effective coping and reduce psychological distress showed beneficial effects in cancer patients.²⁰

In some human study, they showed stress affects pathogenic processes in cancer, such as antiviral defenses, DNA repair, and cellular aging. Moreover, there are many data emphasize on breast cancer. The reason of lack of consistent results might be many cancers are diagnosed only after they have been growing for many years, resulted in one-way-association between stress and the disease onset was difficult to demonstrate.²¹ On the other hand, research based on animal models clearly demonstrated the effect of stress on metastasis and tumor growth.²²

Identifying depression in breast cancer patients

The diagnosis of major depression by DSM-IV (Diagnostic and Statistical Manual of Mental Disorders - fourth edition) criteria includes physical symptoms that may be indistinguishable from the symptoms that occur with the cancer itself or the side effects of treatments. Insomnia, loss of appetite, lack of energy, and loss of concentration play role as confounding factors in the assessment of patient with depression. The proposed solution is by eliminating somatic symptoms from measuring depression in patients with cancer to emphasize psychological symptoms of distress. These symptoms include suicide, guilt, helplessness, and hopelessness.²³ Thus, diagnosing depression in breast cancer needs assessment from mental health professionals.

Cancer treating teams use screening tools for identifying depressive symptoms. Many depression screening tools are available, but only common tools for depression in cancer patients are elaborated. The Profile of Mood States Questionnaire, sixty-five items questionnaire is often used in several studies of mood disturbance and breast cancer. It has Likert-scale in subcategories i.e. depression-dejection, tension-anxiety, anger-hostility, confusion-bewilderment, vigor-activity, and fatigue-inertia. Patient rates his/her symptoms over the past week and a total mood disturbance score is calculated by adding the scores in subcategories.²⁴

Another tool is a visual analogue, from 0–10, made by the National Comprehensive Cancer Centre Distress. It rates overall distress level over the past week. This thermometer is validated for different cancers and in different areas of the world. A score of > 7 on this scale mandates a complete psychiatric evaluation.^{25,26}

The Hospital Anxiety and Depression Scale (HADS) is a reliable and sensitive screening consists of 14 item scale. It is the most common scale to study anxiety and depression in breast cancer patients. Four points Likert-scale is asked to the patients and they need to respond it quickly in order to avoid thinking too long before answering.²⁷

Management of depression in breast cancer patients

Management of depression in breast cancer patients includes psychotherapy, pharmacotherapy or combination if necessary (Table 2). Type of treatment depends on severity of depression, patient's compliance, and nature of interactions between antidepressants and anti-neoplastic agents.

A. Psychotherapy

Behavioral therapies alone can diminish the symptoms of depression in cancer patients. Intervention group with encouraging group cohesion, members' connection, and more sessions are associated with decrease in psychological distress.²⁸ Couple-based psychosocial interventions for women with their partners may be a particular assistance to both partners in their relationship and emotional support from the partner is important in women's adjustment.¹¹

Psychoeducation

Psychoeducation provides medical information about causes, prognosis, and treatment strategies of cancer. These educational programs help to improve problem solving skills and communication between medical team and the patient. Randomized controlled trial (RCT) showed reduction in depression, anger, and fatigue ($p < 0.001$, $p < 0.001$, $p = 0.069$, respectively) in cancer patients who received psychoeducation.²⁹

Cognitive behavior therapy

This psychotherapy enables patient to identify and reduce negative thoughts and eventually increase positive adaptive behaviors. Cognitive behavior therapy (CBT) is also effective in patient with metastatic breast cancer. Significant improvement was noted in depressed mood, anxiety, and sleeping behavior in 17 women experiencing menopausal symptoms who received CBT after completing breast cancer treatment. Hot flushes and night sweats reduced significantly following the treatment (38% reduction in frequency and 49% in problem rating) and improvements were maintained at third months follow-up (49% reduction in frequency and 59% in problem rating).³⁰

Table 2. Therapeutic modalities for depression in breast cancer

Intervention	Subjects	Method	Results	Studies	Year	Ref	Remark
PSYCHOTHERAPY							
Psychoeducation	203 subjects of breast cancer patients after initial treatment	RCT	Significant reduction in anxiety ($p = 0.001$), anger ($p < 0.001$), depression ($p < 0.001$), and fatigue ($p = 0.069$), an improvement in vigor ($p = 0.109$), interpersonal relationships ($p = 0.166$), emotional and role functioning ($p = 0.006$), in health status and fatigue level ($p = 0.141$) among group participants.	Dolbreault S, et al	2009	29	To improve problem solving skills and communication.
<i>Cognitive behavior Therapy</i>	17 patients with metastatic breast cancer after completing breast cancer treatment	Cohort study	Hot flushes and night sweats reduced significantly following the treatment (38% reduction in frequency, $p < 0.03$ and 49% in problem rating, $p < 0.001$) and improvements were maintained at 3 months follow-up (49% reduction in frequency, $p = 0.02$ and 59% in problem rating, $p < 0.001$).	Hunter, et al	2009	30	To identify and reduce negative thoughts and eventually increase adaptive positive behaviors.
<i>Supportive Expressive Therapy</i>	353 women within one year of diagnosis with primary breast cancer for 12-week supportive-expressive group therapy	RCT	There was neither a main effect for treatment in the model using imputed data [F (1,252) = 0.85, $p = 0.36$] and in the reduced model [F (1,211) = 1.8, $p = 0.18$], nor an interaction effect for treatment by level of distress in the model with imputed data [F (18,252) = 0.46, $p = 0.50$] and the reduced model [F (15,211) = 0.52, $p = 0.47$].	Classen CC, et al	2008	31	Social support is an important predictor of better health-related QoL.
<i>Mindfulness Based Stress Reduction (MBSR)</i>	485 women with advanced breast cancer	RCT	SET ameliorated and prevented new DSM-IV depressive disorders ($p = 0.002$), reduced hopeless-helpleness ($p = 0.004$), trauma symptoms ($p = 0.04$), and improved social functioning ($p = 0.03$).	Kissane DW, et al	2007	32	To increase social support thereby improving symptoms control.
	84 female breast cancer patients for 6 week of MBSR	RCT	Compared with usual care, subjects assigned to MBSR (Breast Cancer) had significantly lower (two-sided $p < 0.05$) adjusted mean levels of depression (6.3 vs 9.6), anxiety (28.3 vs 33.0), and fear of recurrence (9.3 vs 11.6) at 6 weeks.	Lengacher, et al	2009	34	Yoga and meditation are used to learn visualization, breathing exercises, and to become aware of the body's reaction to stress and ways of regulating it.
PHARMACOTHERAPY							
<i>Selective Serotonin Reuptake Inhibitors (SSRIs)</i>	computerized search of MEDLINE, using PubMed, for the period from January 1999 to December 2006	Meta-analysis	Practice guidelines for the treatment of patients with major depressive disorder.	Gelenberg AJ, et al.	2010	38	SSRIs are first line agents. SSRI with minimal effect on CYP2D6 metabolism, such as escitalopram preferred.
<i>Serotonin Norepinephrine Reuptake Inhibitors (SNRIs)</i>	13 patients with neuropathic pain following breast cancer treatment	RCT	The average daily pain intensity as reported in the diary (primary outcome) was not significantly reduced by venlafaxine compared with placebo. ($p < 0.05$).	Tasmuth T, et al	2002	40	Preferred in post operative pain syndrome.
<i>Tricyclic Antidepressants (TCAs)</i>	100 patients scheduled for either partial or radical mastectomy with axillary dissection	RCT	Significant decrease in the incidence of chest wall pain (55% vs. 19%, $p = 0.0002$), arm pain (45% vs. 17%, $p = 0.003$), and axilla pain (51% vs. 19%, $p = 0.0009$) between the control group and the venlafaxine group, respectively.	Reuben SS, et al	2004	41	
	179 women with breast cancer randomized to treatment with either the SSRI paroxetine (20-40 mg/day), or the TCA, amitriptyline (75-150 mg/day) for 8-weeks of treatment	RCT	A steady improvement in quality of life was also observed in both groups. There were no clinically significant differences between the groups ($p = 0.996$). In total, 47 (53.4%) patients in the paroxetine group and 53 (59.6%) patients in the amitriptyline group had adverse experiences, the most common of which were the well-recognized side-effects of the antidepressant medications or chemotherapy. Anticholinergic effects were almost twice as frequent in the amitriptyline group (19.1%) compared with paroxetine (11.4%).	Pezzella G, et al	2001	42	Effective drugs, but the cholinergic side effects limit their use.

Supportive expressive therapy

It includes supportive techniques as well as expressive techniques to enhance the client's sense of mastery in relation to on-going problems and hence primarily targets symptomatic relief. This therapy aims to increase social support thereby improving control of symptom and to enhance communication between medical team and the patient. Affective expression helps leading the therapist to problems that should be addressed. Evidence of the effectiveness of supportive expressive therapy (SET) in breast cancer patients showed inconsistent results. A study of 353 breast cancer women at University of Toronto, Canada with 12 week of SET found no evidence in reducing distress,³¹ while in New York, a study of 485 advanced breast cancer women with SET showed an improvement of the quality of life (QoL) ($p = 0.003$).³²

The quality of the social support received by survivor is also an important predictor of better health-related QoL. Thus, psychosocial intervention that was aimed at increasing social support beyond the acute phase of the treatment may have a vital role in on-going care of breast cancer survivors.³³

Mindfulness based stress reduction

It is a standardized form of yoga and meditation where patients learn visualization, breathing exercise, and becoming aware of the body's reaction to stress and ways of regulating it. In an RCT of 84 female breast cancer patients, a 6-weeks mindfulness based stress reduction (MBSR) improved physical functioning and reduced distress related to cancer as well as fear of cancer recurrence.³⁴

B. Pharmacotherapy

Selective serotonin reuptake inhibitors

Expert consensus guideline on treating depression and related symptoms specifically in women with breast cancer recommended selective serotonin reuptake inhibitors (SSRIs) as the first line agent.³⁵ The interaction between SSRIs and chemotherapeutic agents is a concern. Tamoxifen (10 mg twice daily or 20 mg once daily orally for 5 years) decreased the rate of death from breast cancer in hormone receptor positive breast cancers.³⁶ Endoxifen, a potent antiestrogen, is an active metabolite of tamoxifen via cytochrome P450-2D6 (CYP2D6). SSRIs can varyingly inhibit CYP2D6. Paroxetine and fluoxetine were found to be strong inhibitors of CYP2D6 which led to low levels of endoxifen. Weaker inhibitors are sertraline

and escitalopram (10-20 mg/day, oral).³⁷ According to American Psychiatric Association's guideline for treatment of major depressive disorder (MDD), depressed breast cancer patients who received tamoxifen should be generally treated with an antidepressant that has minimal effect on CYP2D6 metabolism. These medications are usually given till remission and continued up to 6-9 months to prevent relapse.³⁸

Serotonin norepinephrine reuptake inhibitors

Venlafaxine (75-375 mg/day, oral) and desvenlafaxine (50-400 mg/day, oral) are SNRIs. These medications are started with low dose and gradually increased to optimal level. Starting dose of venlafaxine is 75 mg/day orally and desvenlafaxine is 50 mg/day.³⁸ Post-operative pain syndrome which occurs in almost half of the patients undergo mastectomy or breast reconstruction is characterized by burning, stabbing pain in the axilla, arm and chest wall of the affected side. It also has poor response to opioids.³⁹ In a study, venlafaxine significantly improved pain relief compared to placebo and is associated with lower incidence of pain in the chest wall, arm and axillary region. But, it has shown mixed results in minimizing anxiety or depression in different studies.^{40,41}

Tricyclic antidepressants

Though tricyclic antidepressants (TCAs) are proved to be effective in treating depression in breast cancer patients, their side effects notably cholinergic effects, limit their use as antidepressants, especially when compared with SSRI treatments.⁴²

In all stages of breast cancer, patients are at risk for depression. Symptoms and severity of depression depend on coping styles, family support, age at diagnosis of cancer, changes in appearance, as well as the anti-neoplastic treatment. Depression in cancer patients may mimic side effects of cancer therapy and often mislead the treating team. HADS scale is recommended for screening tools of depression in clinical settings. Psychotherapy and pharmacotherapy are effective for these patients. SSRIs that have effects on CYP2D6 metabolism will influence the pharmacotherapy of the patients. Thus, antidepressants such as escitalopram, venlafaxine or desvenlafaxine are preferred. Moreover, desvenlafaxine has additional advantage in patients with post-operative pain syndromes.

Depression does not only play significant role in cancer treatment adherence, but also affects quality of life in breast cancer survivors. Treatment of depression in these patients has positive impact on outcomes. Thus,

women with breast cancer of any stage should be screened and treated for depression to increase survival and improve quality of life. Further research is needed to have a better insight into etiological factors and improvised treatment methods among these patients.

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