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BREAST CANCER AND MENTAL HEALTH: UNDERSTANDING THE LINK TO DEPRESSION IN AN INDIAN SCENARIO

Dr. Sivasankar Perumal — Psychiatry Trainee, Unit of Psychiatry, Norfolk and Suffolk NHS Foundation Trust, United Kingdom

Dr. Anichavezhi Devendran* — Visiting Researcher, School of Biological Sciences, University of Essex, United Kingdom *Corresponding Author

ABSTRACT Depression can occur in more than 15% of patients with breast cancer (BC), affecting a person psychologically and emotionally. The objective of this chapter is to understand the pathophysiology, diagnosis and management. Various screening tools are used to identify depression in addition to using the diagnostic criteria from Diagnostic and Statistical Manual of Mental Disorders (DSM) and International Classification of Diseases (ICD-10). There is twice the risk of suicide in cancer patients for which Ketamine is successfully trialed to reduce suicidal ideation. This aside, non-pharmacological methods of cognitive behavioral therapy and motivational interviewing are explored. Hence, the use of multidisciplinary care delivery models combined with pharmacological and psychological treatments to improve anxiety, pain quality of life are briefly discussed.

KEYWORDS : Diagnostic and Statistical Manual of Mental Disorders (DSM), International Classification of Diseases (ICD-10), psychostimulants, suicide, cognitive behavioral therapy.

1. INTRODUCTION

Breast cancer (BC) is the most commonly diagnosed malignancy worldwide and the leading cause of death in women. It is the leading cause of global cancer incidence in 2020, with an estimated 2.3 million new cases, representing 11.7% of all tumors [1] [2]. The rate of incidence was found to be 25.8 in 100,000 women and the mortality rate is 12.7 per 100,000 women [3]. As per the Indian Council of Medical Research- Population Based Cancer Registries (ICMR-PBCR) data, breast cancer is the commonest cancer among women in the urban registries of Delhi, Mumbai, Ahmedabad, Kolkata, and Trivandrum where it constitutes >30% of all cancers in women.

People often discuss the physical symptoms than mental wellbeing. Treatment methods like mastectomy, chemotherapy, can lead to low self-esteem, hopelessness and body esteem. This aside, Anxiety and depression can present during the course of the disease leading to a poorer quality of life.

2. Prevalence

There is a wide range of BC prevalence from 2.0-43.5%. Studies conducted by Vahdaninia et al. [4] and Maass et al. [5] found that depression was higher in the first year after diagnosis. To elaborate furthermore, they reported a 32.8% prevalence of depression in a very large cohort of cancer patients. It was also found that there was a 40% prevalence of anxiety and depression in cancer patients who faced disease recurrence. Besides, Reich et al. (2008) [6] reported 42% prevalence of different mental health issues and out of which 35.7% of the BC patients experienced anxiety or depression, with major depression was found to be around 7%, mild depression around 25.6%, and anxiety disorder around 6.2% of prevalence.

3. Pathophysiology

It is challenging to understand the biology of major depressive disorder due to the clinical and etiological variability of the condition. The hypotheses are supported by research on stress hormones, neurotransmitters and circadian rhythms (figure 1).

4. Psychosocial

Stress due to cancer overwhelms a person's capacity to cope with life events resulting in depression, and feelings of hopelessness. People with poor communication with medical professionals, unhelpful coping mechanisms, and past mental illness are at high risk of getting depression. Being optimistic and emotional support from friends and family can prevent depression [4] (figure 2).

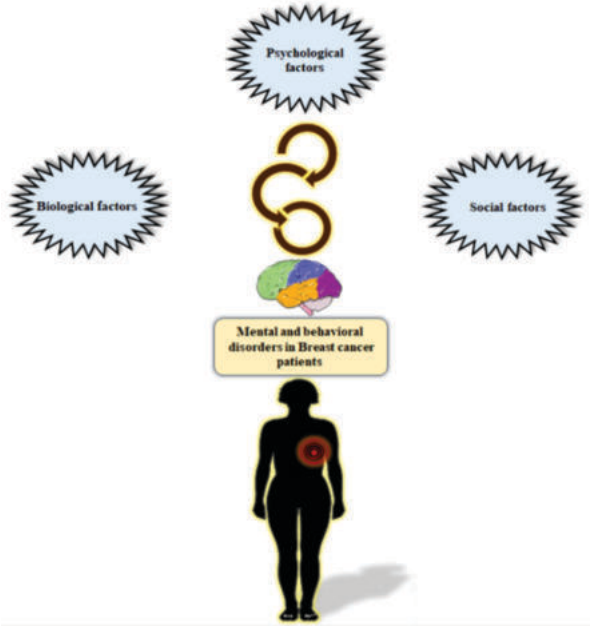

Figure 1. Several Factors Like Biological, Psychological And Social Contribute To The Mental And Behavioural Disorders In Breast Cancer (BC)

Figure 2. Some Of The Most Common Issues Observed In The Practical, Psychological, Emotional, Spiritual, Informational, Social And Physical Lifestyle Among BC Patients

5. Cytokines:

Evidence suggest that biological processes are a cause for depression in cancer. Damage-associated molecular patterns (DAMPs), of tissue damaged by surgery, chemotherapy, or radiotherapy, bind to pattern recognition receptors (PRRs) on leukocytes, particularly macrophages. This causes the expression of the transcription factor nuclear factor- (NF) and the production of a variety of pro-inflammatory cytokines, such as interleukin-1 (IL1), interferon (INF), IL-6, and tumour necrosis factor (TNF) [7]. Additionally, some chemo-therapeutic drugs can directly stimulate NF□□ and ionising radiation without causing tissue damage, which boosts the expression of inflammatory mediators, psychosocial stress has been demonstrated to increase NF□□ expression in healthy patients [8].

Through the activation of p38 mitogen-activated protein kinase (MAPK), Tumour necrosis factor (TNF), Interleukin-1 (IL-1), and other cytokines increase the activity and expression of serotonin (5-hydroxytryptamine; 5HT) and noradrenaline (NA) reuptake transporters. This effectively decreases the synaptic concentrations of 5-hydroxytryptamine receptors (5HT) and noradrenaline (NA), which may result in depressed behaviour [9]. Moreover, the levels of the pro-inflammatory cytokines increases releasing the hormone corticotrophin (CRH). The CRH itself can cause behavioural changes including those observed in depression [9].

5.1 Role of Corticotrophin (CRH):

CRH induces the secretion of pituitary corticotrophin, to release cortisol into the plasma. Compared to men, women generally show greater stress responsiveness than men, which is consistent with the greater incidence of major depression among women [10]. Hypothalamic-pituitary-adrenal axis (HPA) was not often dysfunctional in patients with Major Depressive Disorder (MDD) [11]. However, some subjects with MDD showed abnormalities of the CRH system. Furthermore, evidence suggests that levels of CRH in the cerebrospinal fluid were elevated in some depressed subjects [12]. On the other hand, in limbic brain regions associated with depression, the post-mortem investigations found more CRH-secreting neurons, which is a compensatory reaction to the elevated CRH concentrations.

5.2 Tryptophan

It is well known that the depressed patients' brains have lower tryptophan levels than the monoamine levels. The pro-inflammatory cytokines, particularly TNF, boost the activity of the tryptophan-degrading enzyme, viz., indolamine 2, 3-dioxygenase (IDO).

6. Autonomic Nervous System

Prolonged stress in cancer can lead to the stimulation of sympathetic nervous system (SNS) and hypothalamic-pituitary-adrenal (HPA) axis, whereas the parasympathetic nervous system (PSNS) is inhibited. The chronic SNS stimulation increased Nor-Adrenaline release, which binds to adrenergic receptors on macrophages and thereupon triggers NFκβ activation and cytokine production, further lowering 5HT and NA levels. However, the PSNS is inhibited in a chronic stress state, instead leading to increased cytokine formation, which acts to further alter the neurotransmitter levels [13].

Figure 3. The BC Pathophysiology And The Outcomes That Affect The Mental Stature In BC Patients

7. Therapeutic Drugs:

Haloperidol, a dopamine antagonist receptor 2 is used occasionally to treat nausea secondary to chemotherapy that has been linked to depression [14]. According to reports, up to 50% of patients who receive immunotherapy drugs, such as INF, for various malignancies experience depression [9].

8. Symptoms

According to the Diagnostic and Statistical Manual of Mental Disorders (DSM), a patient must exhibit either a depressed mood or lack of interest in activities for at least two weeks in order to be diagnosed with a depressive illness. Other symptoms include decreased attention, low self-esteem, guilt and unworthiness thoughts, pessimistic outlooks on the future, thoughts or actions related to self-harm or suicide, poor sleep, and decreased eating. Additionally, the symptoms must be severe enough to cause significant distress or impairment and cannot be the result of a disease or substance's physiological side effects [15]. Reduced appetite and poor cognition may be more useful symptoms in diagnosing depression in cancer. Feelings of guilt and failure are also lower among depressed cancer patients, at 4%, compared with depressed but otherwise healthy patients, at 56.5% [16].

9. Diagnosis:

Depression is frequently underdiagnosed due to the difficulty in distinguishing symptoms such as sadness and loss of interest, from a "realistic" response to physical illness. Patients or the clinicians may be sceptical about the efficacy and tolerability of antidepressant and various alternative diagnostic approaches have been proposed to diminish the effect of confounding somatic symptoms as listed below [17]:

a. Inclusive approach: All depressive symptoms should count regardless of whether alternative explanations for the symptoms exist or not.
b. Exclusive approach: Ignore any symptoms that might be otherwise explained.
c. Etiological approach: Ignore items if they are thought to be more likely a result of comorbid medical illness.
d. Substitutive approach: Replace those items that are most likely confounded from the diagnostic workup with other symptoms considered less controversial.

Although no specific statements about the sensitivity and specificity of each approach can be made in the absence of a reliable criterion measure, overall, the results appear consistent and may represent a reasonable balance between over-inclusivity and over-exclusivity in the oncology setting [18]. The Screening scales have been most widely used to screen for depression in medically ill are as follows:

1) The Centre for Epidemiologic Studies Depression Scale (CES-D)
2) The Hospital Anxiety and Depression Scale (HADS)
3) Beck Depression Inventory-II (BDI-II.
4) The Patient Health Questionnaire (PHQ).

Additionally, the Single-item and very brief screening scales like Schedule for Affective Disorders and Schizophrenia (SADS), or a subset of questions from common scale (e.g. the Montgomery-Asberg Depression Rating Scale: MADRS, Patient Health Questionnaire-2: PHQ-2) have some utility.

10. Treatment:

The effectiveness of treatment of depression has been the focus of numerous systemic and meta-analysis. Collaborative care characterized by active collaboration between psychiatrists, and other medical who provide psychological interventions (e.g., problem-solving therapy: PST)) and monitors treatment compliance and outcomes [19] [20] have led to long-term remission.

Besides, the primary goal in treating depression in cancer patients is to control pain.

10.1 Antidepressants:
The Selective serotonin reuptake inhibitors (SSRI) like the tricyclic antidepressants (TCA) and Psychostimulants are the groups of medication, which are mainly used to treat depression in cancer.

10.1.2. Selective Serotonin Reuptake Inhibitors (SSRI):
The Selective serotonin reuptake inhibitors are safe and effective with minimal side effects. However, due to the side effects of nausea and gastrointestinal distress, consideration is needed in patients receiving chemotherapy and radiotherapy as it may worsen the symptoms [21]. Fluoxetine is less tolerated when compared to sertraline and paroxetine due to the long half-life. SSRI'S are safe in patients with cardiac disease and easy to titrate.

Moreover, due to the inhibition of cytochrome P4502D6 (CYP2D6), it can interact with the metabolism of Tamoxifen thereby reducing the active metabolite endoxifen.

10.1.3. Tricyclic Antidepressants (TCA):
Tricyclic antidepressants are effective in treating neuropathic pain. They are not well tolerated by terminally ill due to their anticholinergic side effects like dry mouth, constipation and delirium, which can worsen with chemotherapeutic agents.

10.1. 4. Psychostimulants:
Due to the slow onset of response from the first line medications which usually takes 1-2 weeks to see any noticeable change in mood, it is not helpful to use SSRI'S OR TCA'S in terminally ill patients. Prescribing psychostimulants like Methylphenidate, Dextroamphetamine and Pemoline can be beneficial as they act rapidly and are well tolerated. This can reduce distress and help cope effectively. Psychostimulants can be used as an adjunct analgesics, counter opioid induced fatigue, improve appetite and energy [22].

10.1.5. Ketamine:
Clinical trials show that a single dose of ketamine can have short-term benefits in the acute treatment of suicidal ideas. Though there is a doubt in its usage, where the potential to be used in clinical care for suicidal patients cannot be ignored [23].

Figure 4. Effects of Different Therapeutic Regimen Used for the Treatment of Depression Among BC Patients

11. Psychosocial Therapy:
Various approaches have been used like the cognitive behavioural therapy (CBT), problem solving therapy (PST), acceptance and commitment therapy (ACT) [24]. Other methods like Cognitive and Behavioural Cancer Stress Management (CBCSM) interventions, Supportive-Expressive Therapy (SET), Meaning-Centred Psychotherapy (MCP) have also been tried. The objective is to relax the patient, reduce the mental tension and improve the quality of life It is important to take into consideration the timing, goals and frequency of the therapy needed to maintain therapeutic relationship, assess suicidality and treatment adherence.

The most useful CBT program designed for breast cancer patients is the Cognitive Behaviour Stress Management (CBSM) [25]. Being the most studied interventions of all therapies, it improves coping skills and emotional expression, increasing awareness to one's stress response, and teaching anxiety-reduction and cognitive restructuring skill.

12. Motivational Interviewing:
Motivational interviewing uses the technique of patient centred approach developing the patient's motivations for behaviour change through open-ended discussions [26]. It helps patients to develop their own solutions and include the change in their daily life. This is in contrast to the other techniques like cognitive behavioural therapy, social cognitive theory and trans theoretical model which use predetermined strategies to identify and focus on the change based on the patient's readiness.

13. Suicide:
The relative risk of suicide in depressed patients secondary to cancer is two times more than the general population. Factors such as substance abuse, hopelessness, lack of social support, and advanced state of disease increase such risk. Studies have shown that solitary, advanced-stage breast cancer patients from low socioeconomic backgrounds are more likely to commit suicide [27].

14. Sexual Dysfunction:
The removal of the breast due to cancer presents a risk to the patient's sense of attractiveness, motherhood, and sexuality as well as their body image [28]. Surgery, radiotherapy, chemotherapy, and/or hormonal therapy all have a significant impact on a patient's sexual life. Loss of breast tissue, hair loss, pain, body image, the ability to bear children, affects patients desire to engage in sexual activity.

15. Mortality:
Dysregulation of the hypothalamic-pituitary-adrenal axis, especially diurnal variation in cortisol and melatonin can influence mortality in cancer patients who are depressed, they may not comply with the screening and treatment recommendations [29]. Depressed patients may be less likely than non-depressed patients to recruit, retain and benefit from social support.

16. Conclusions and Future Directions:
Research has shown that the majority of cancer patients do not seek treatment for depression. This was addressed through a new approach called 'Depression Care for People with Cancer' (DCPC) in a randomised trial called SMaRT Oncology-2. Also called the collaborative care model, its core components for depression care are: i) a multi-professional approach to patient care, ii) a structured management plan tailored to depression symptom severity, iii) scheduled patient follow-ups and iv) enhanced inter-professional communication [30,31]. Apart from depression, the model, also improved anxiety, pain, fatigue, functioning. Though there are limitations, it gives hope that depression can be treated even in patients with poorer prognosis improving the overall quality of life.

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