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# Pathogenesis, Consequences, and Therapy of Depression in Cancer Patients: A Review

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**ABSTRACT**
More than 10% of cancer patients also have depression, which is a common comorbidity. A cancer diagnosis is a major life-changing event that causes a lot of mental and emotional stress. Non-pathological melancholy may be a common reaction to a cancer diagnosis, but stress that exceeds the capacity of the patient's coping systems may lead to severe depressive disorder. Along with the apparent psychosocial components of depression, the current study also examines its biological causes, such as tissue damage, inflammatory mediators, and the chronic stress response, as well as how these immunological and endocrine pathways may contribute to depression in cancer. The investigation of potential iatrogenic depression in cancer patients continues. In order to improve quality of life and decrease mortality, depression in cancer patients must be recognised and treated. We quickly describe the most used clinical and anticipated biochemical screening methods for depression in cancer. Although there is a dearth of research on the most effective care of depression in cancer, the best mix of medicines is unknown. Interventions employed will differ for each patient but may include psychosocial therapies or medication. Given the frequent side effects of chemotherapy (such as nausea) and the need to prevent significant interactions, such as decreasing the efficacy of chemotherapeutic medications, great consideration should be given to antidepressant choice. The potential connection between the chronic stress response, which may put patients at risk for depression, and the likelihood of dying from cancer is also investigated. Future research could lead to the creation of quicker and more effective treatments for depression in cancer due to the complex interactions between the endocrine, neurological, and immune systems that are still being fully understood.

**Keywords:** depression, progression, cancer, mental disorder, pathogenesis, diagnosis, modulation.

## 1. INTRODUCTION

Patients experience a significant deal of distress when given the potentially fatal and feared diagnosis of cancer. Compared to non-neoplastic disorders with worse prognoses, cancer diagnoses cause more distress (1). Anxiety, sadness, or both may result from cancer patients experiencing high levels of emotional discomfort over an extended length of time (2). Two thirds of cancer patients who also have depression report clinically significant levels of anxiety, making this mixed symptomatology quite prevalent (3).



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Depression affects patient outcomes and lowers quality of life (QOL), and is associated with increased cancer mortality rates (4,5). According to a meta-analysis, people with minor or major depression had a 39% higher risk of dying, while those with even mild symptoms may have a 25% higher risk (6). More than 70% of oncologists and 85% of patients believe that mood impacts the progression of cancer, demonstrating the importance of the relationship between mood and mental health and cancer (7).

It is believed that cancer patients have a rate of depression that is up to three times higher than the general population (2). While palliative care wards have reported depression rates as high as 49.0%, studies utilising Diagnostic and Statistical Manual of Mental Disorders (DSM) criteria (8) for major depressive disorder (MDD) have found a range of prevalences ranging from 2.0-43.5% (9,10). (11). The vast range of reported prevalences could be brought on by various evaluation methods, different patient types interviewed, different age groups, different gender ratios, inpatient status, and other variables. The prevalence of depression was estimated to be 10.8% in a research by Linden et al. (2) and 12.9% in a thorough literature analysis by Ng et al. (12) that included rates from >9,000 individuals in a variety of contexts and ages. Additionally, 16% more people are said to have subclinical yet harmful depression (2,5).

Depression rates are also influenced by the location of the original cancer, being highest in pancreatic and lung tumours and lowest in invasive skin cancer (2). Age also affects prevalence. While several cancers in adults were inversely correlated with age and depression, data suggests that children and adolescents with cancer are not more depressed than healthy controls (13,14). (2). In some cancer kinds, female patients were shown to be two to three times more likely than male patients to have depression (2). Psychological stress and sadness levels change over the course of the illness as well, reaching their peak right after diagnosis (2). However, it was found that the 4% risk of depression among cancer survivors five years after diagnosis was comparable to that of the general population (15).

Depression levels have also been linked to metastatic disease and cancer pain (11). Patients with high levels of pain have a significantly higher prevalence of depression than those with low levels of pain; one study found that 33% of patients with high levels of pain had depression, compared to 13% of patients with low levels of pain, suggesting that pain may be a contributing factor to depression (16).

**Symptoms and Diagnosis**

The patient must have either a sad mood or a decreased level of interest or enjoyment in activities for at least two weeks in order to receive the DSM diagnosis of MDD. Additionally, four or more of the following requirements must be met:

Significant changes in weight, hypersomnia or sleeplessness, psychomotor changes, exhaustion, remorse or worthlessness sentiments, poor cognition or attention, and persistent thoughts of suicide are all risk factors for these conditions. The symptoms must also significantly disturb or impede the patient, and they cannot be brought on by a substance or a disease's physiological side effects (8).

Clinical professionals may mistake the bodily signs of depression, such as exhaustion, lack of appetite, weight shift, and impaired cognition, for side effects of cancer therapy or other illnesses, which results in a reduction in the disorder's identification. In one study, even after controlling for cancer pain and physical functionality, it was discovered that changes in appetite and diminished cognitive performance were positively associated with anhedonia, although sleep problems and weariness were not. This implies that decreased appetite and poor cognition may be better indicators of depression in cancer patients (17).

 

Additionally, there is a decreased prevalence of guilt and failure feelings among depressed cancer patients (4% vs. 56.5% for sad but otherwise healthy individuals) (18). Given the severe physical and psychological stress on patients, it may be normal for some of the symptoms listed above to be present, making diagnosis difficult.

Other behavioural problems, such as trouble sleeping, poor cognition, anorexia, social disengagement, and weariness, may also plague patients (19,20). Screening. Screening is crucial to identifying individuals who need further support because they are depressed (4,5).

Seven questions about depressive symptoms are included in the self-administered Hospital Anxiety and Depression Scale – Depression (HADS–D) (21) screening questionnaire. The patient rates each question from 0 to 3 on a scale of 1 to 3. Scores between 8 and 11 are highly diagnostic of depression, while scores between 8 and 10 are indicative of probable depression (21). According to a study measuring interleukin-6 (IL-6) levels and relative diurnal cortisol variation in depressed cancer patients, IL-6 levels are seven times higher in those with depression compared to those without depression (18.7 pg/ml vs. 2.7 pg/ml), while relative diurnal cortisol variation is six times lower (11.7% vs. 60.6%). Diurnal cortisol variation screening tests for depression in cancer patients had the highest specificity and sensitivity, at 88% and 81%, respectively; these tests may thus be helpful in identifying depression in cancer patients (22).

**Pathogenesis**

A complex condition, depression in cancer patients has behavioural, biological, and even iatrogenic origins. social and psychological. The spectrum of depression includes non-pathological melancholy, adjustment disorder, subclinical depression, and severe depression.

Stress that overwhelms a person's capacity to cope with life events may result in depression, which is characterised by a consistently down mood, despair, anhedonia, and feelings of hopelessness.

A grim prognosis or the tremendous unpredictability that patients experience may be the cause of emotional stress. A cancer diagnosis and treatment may have a detrimental impact on a patient's career, family, physical appearance, abilities, independence, and finances, which makes the situation worse. People who have poor communication with medical professionals, unhelpful coping mechanisms, and a history of mental illness are at an especially high risk of getting depression (10). An optimistic outlook and a lot of emotional support from friends and family can prevent depression (2). Inflammation. There is evidence that suggests biological processes may be significant in addition to the obvious emotional and sociological aspects of depression in cancer.

Damage-associated molecular patterns (DAMPs), which are produced when tissue is 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 (23). Additionally, NF can be directly stimulated by some chemotherapeutic drugs and ionising radiation without causing tissue damage, which boosts the expression of inflammatory mediators (24). Additionally, psychosocial stress has been demonstrated to increase NF-expression in healthy patients (25).

Through activation of the p38 mitogen-activated protein kinase, TNF, IL-1, and other cytokines have also been found to increase the activity and expression of serotonin (5-hydroxytryptamine; 5HT) and noradrenaline (NA) reuptake transporters (MAPK). This effectively reduces the levels of 5HT and NA in synapses, which might result in depressed

 

behaviours (26–28). Additionally, corticotropin-releasing hormone release is increased by proinflammatory cytokines (CRH). Changes in behaviour, including those seen in depression, can be brought on by CRH itself (29). Additionally, these cytokines lower levels of neurotrophic factors that are essential for neurogenesis, such as brain-derived neurotrophic factor (BDNF). Depression's aetiology has been linked to low levels of BDNF and neurogenesis (30).

INF has been found to lower the expression of dopamine (DA)2 receptors and inhibit striatal DA release in non-human monkey studies, resulting in anhedonia. INF also leads to decreased conversion of phenylalanine to tyrosine, which results in reduced downstream synthesis of DA in the brain and, possibly, depressed symptoms (31), although the mechanisms underlying this and any relevant pharmaceutical solutions have to be clarified (32). It has been demonstrated that pro-inflammatory cytokines, particularly TNF, boost the activity of the tryptophan-degrading enzyme indolamine 2,3-dioxygenase (IDO). Since tryptophan is the chemical precursor to 5 HT, its degradation lowers the levels of 5 HT (33). It is well known that depressed patients' brains have lower tryptophan levels than they do monoamine levels (34).

The development of neurodegenerative tryptophan catabolites is another result of IDO induction (TRYCATs). These TRYCATs, which include kynurenine and quinolinic acid and are proinflammatory and neurotoxic in the brain, may also be crucial in the treatment of depression in cancer patients. While kynurenine has been shown to be anxiogenic, quinolinic acid is a powerful N-methyl-D-aspartate (NMDA) receptor agonist that can cause lipid peroxidation in neurons by excitotoxicity (35). Quinolinic acid concentrations have been found to be higher in various areas of the anterior cingulate cortex in patients with severe depression. Depression has been linked to neurotoxin exposure and brain ageing, particularly in the hippocampus (36).

**Chronic stress:** Chronic stress is a condition that results from having to deal with the physical and mental strain of a cancer diagnosis and treatment. The hypothalamic-pituitary-adrenal (HPA) axis is activated, the sympathetic nervous system (SNS) is stimulated, and the parasympathetic nervous system (PSNS) is suppressed during times of stress (26,27,37–39). The HPA axis should be stimulated, which should trigger the release of endogenous glucocorticoids, strong anti-inflammatory compounds that typically stop the synthesis of pro-inflammatory cytokines. However, p38 MAPK inactivates the intracellular glucocorticoid receptor (GCR) de leukocytes as a result of PRR activation by DAMPs; as a result, the anti-inflammatory impact of glucocorticoids is diminished and cytokine expression is elevated (23,40). The remaining active GCRs may become less sensitive as a result of proinflammatory cytokines, which could further reduce the anti-inflammatory effect of glucocorticoids and increase cytokine production (41). Additionally, the increased NA released as a result of prolonged SNS stimulation binds to adrenergic receptors on macrophages, which further activates NF and induces the production of cytokines, resulting in additional drops in 5HT and NA levels (27,28). Pro-inflammatory cytokine production should typically be inhibited by PSNS activity; acetylcholine binds to nicotinic receptors on leukocytes and prevents the synthesis of NF (38). Chronic stress, however, inhibits the PSNS, which causes an increase in cytokine production that further modifies the levels of neurotransmitters (38,39).

**Medications:** There is evidence that certain drugs can make cancer patients experience symptoms similar to depression. Haloperidol, a DA receptor 2 antagonist, inhibits

 

dopaminergic transmission in the brain and has been connected to the emergence of depressed symptoms. It is occasionally used to treat chemotherapy-related nausea (42). According to reports, up to 50% of patients who receive immunotherapy drugs, such as INF, for various malignancies experience depression (26–28).

**Implications**

**Chemotherapy and the medical community:** Only 51% of the study group (breast cancer patients with depression) accepted and started chemotherapy, compared to 92% of the control group (breast cancer patients without depression), in a cohort study looking at breast cancer outcomes in patients with depression (4). Depression has an impact on treatment adherence, leads to subpar results, and increases mortality (4,5).

Depression worsens physical symptoms in cancer patients, which lowers QOL significantly and worsens the toll the disease takes on patients and their families (2,43). For instance, patients receiving treatment for breast cancer experienced higher pre-chemotherapy levels of fatigue, depression, and sleep problems throughout treatment, which had substantial and detrimental consequences on their quality of life (QOL) (44). Depression in cancer patients lengthens hospital stays and uses more resources, resulting in higher healthcare costs (45). In addition, depressed cancer patients have a higher risk of suicide than the general populace (46).

**Depression and the progression of cancer**: Compared to patients who are not depressed, cancer patients who are depressed have a higher probability of dying (5). Evidence from animal studies and human studies suggests that the chronic stress response, which may contribute to the development of depression in cancer, may also contribute to increased cancer invasiveness, decreased tumour surveillance by the body, increased angiogenesis, decreased tumour suppressor gene activity, and reduced cellular apoptosis. This is true even though treatment non-participation accounts for some of the increased risk (6,47-51).

**Immune control:** It is believed that a variety of immunological systems contribute to depressed individuals' higher mortality risk as compared to non-depressed patients (6). Depression decreases the number of circulating natural killer (NK) cells in otherwise healthy adults, and it is anticipated that this will also occur in cancer patients. NK cells are generally involved in tumour monitoring (47). Depressed and anxious states were linked to considerably lower levels of T helper 1 cells, cytotoxic T lymphocytes, and interferon (INF) release in the peripheral blood and tumour microenvironment in ovarian cancer patients. In one study on mice, the chronically stressed group was found to have a greater probability of developing squamous cell carcinoma than the non-stressed group when exposed to groups of ultraviolet radiation-sensitive mice (SKH1 hairless mice). The stressed group had a shorter delay before the first tumour appeared, decreased INF expression, higher levels of circulating and infiltrating regulatory T cells, and lower levels of T helper cell infiltration (47). Therefore, ongoing stress decreases anti-tumor lymphocyte and NK cell activity while increasing immunosuppression, which also weakens the immune system's capacity to combat cancer.

**Manipulation of genes:** Another mouse investigation found that the p53 tumour suppressor gene was interfered with when the SNS was repeatedly stimulated under prolonged stress. It was also believed that activating the HPA axis would result in elevated levels of glucocorticoids and systemic increases in the production of p53 inhibitors (namely MDM2).


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Chronic stress decreases p53's normally essential tumour suppressor and anti-angiogenic activities. Catecholamines have been linked to boosting tumour growth in murine prostate cancer models of chronic stress by phosphorylating and inactivating the proapoptotic protein Bcl-2-associated death promoter.

**Invasion and angiogenesis:** Chronic stress elevated tissue catecholamine levels in an ovarian cancer model, which in turn increased the expression of angiogenic proteins (including vascular endothelial growth factor) and the production of pro-invasive enzymes (such as matrix metalloproteinases 2 and 9). Chronic stress may promote angiogenesis and increase some tumours' invasiveness, which would raise the burden of tumours.

**Management**

**Rationale:** In order to enhance QOL and survival in cancer patients, depression must be adequately treated (4,5). It has been shown that individuals with metastatic breast cancer who receive treatment for their depression and see improvement in their depressive symptoms during the first year have a median survival time that is 28.5 months longer than those who do not. Although medication and psychosocial interventions are both successful in treating cancer-related depression, the best way to deliver these treatments remains uncertain, necessitating additional research. Each patient will probably require a different approach to managing their depression.

**Medications:** Tricyclic antidepressants (TCAs) and selective serotonin reuptake inhibitors (SSRIs) are the two main kinds of drugs used to treat depression in cancer patients (12). Although the precise mechanisms of action of these medications are not entirely understood, it is believed that they induce adaptative changes in the brain and gradually boost 5HT neurotransmission to improve mood (26).

Compared to SSRIs, TCAs have more side effects and a higher risk of overdose. However, due to a dearth of studies, a meta-analysis revealed no support for recommending one antidepressant class over another in cancer. When prescribed to patients undergoing chemotherapy or radiation therapy, SSRIs should be used with caution because they frequently exacerbate vomiting and nausea, and TCAs' anticholinergic actions may make chemotherapy-related delirium worse (26).

**Terminally ill patients:** Given that traditional antidepressants have a delayed onset of action, using them in patients with terminal cancer may not be a prudent choice (12,53,54). This idea was reinforced by an observational study that found that, when given to terminally ill sad cancer patients, the antidepressants that are currently prescribed have minimal impact on their depression levels. Methylphenidate may be a good substitute for traditional antidepressants because it showed moderate to significant relief in depression symptoms in a study in just two days for 73% of depressed cancer patients . Physiological tolerance quickly develops, and doses must be raised, despite the fact that methylphenidate experiments have proven encouraging. Because it inhibits NMDA receptors, ketamine has lately been investigated for its quick and powerful antidepressant effects . For cancer patients who are towards the end of their lives and need quick relief from their depression, ketamine has been recommended as a treatment. Larger randomised trials are required to evaluate the effectiveness of ketamine in treating depression in terminal patients; a trial in a single patient with advanced cancer, however, had initially promising but short-lived benefits.

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**Interactions:** By slowing down the metabolism of the antidepressants or by the cancer treatments' own additive effects, chemotherapeutics may combine with antidepressants and lead to nervous system toxicity. Certain antidepressants may impair the effectiveness of chemotherapy medications. An illustration of this is the interaction of several SSRIs with tamoxifen, which decreases the conversion of tamoxifen to its active metabolite, endoxifen, by blocking the hepatic CYP2D6 enzyme and is taken simultaneously in 20–30% of breast cancer patients. This lessens the medication's effectiveness and raises the possibility of a breast cancer relapse. Other SSRIs and herbal remedies containing hypercium (St. John's Wort) may activate the CYP3A4 enzyme, which could result in a decrease in the levels of hepatically excreted anticancer medications or an increase in the levels of medications that are CYP3A4-activated. It is crucial to refrain from changing the dosage of cancer medications since they sometimes have a restricted therapeutic range. Drug interactions must be avoided at all costs.

## 2. CONCLUSION

Cancer patients' depression continues to be an under-recognized comorbidity, with significant consequences for patient suffering, death, and healthcare costs. Depression in cancer patients has a distinct symptomatology and a clear biological aetiology, making it distinct from depression in healthy people. By specifically targeting the vast inflammation and endocrine pathways known to be responsible for depression in cancer patients, innovative anti-inflammatory medications may one day be able to offer more immediate and effective treatment than the antidepressant therapy currently being used. However, more investigation is still needed to determine the best pharmaceutical and psychosocial treatment triads for cancer-related depression.

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