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## *Clinical updates*

### **Depression and anxiety in patients with cancer**

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#### **Box start**

##### **What you need to know**

- Depression affects up to 20%, and anxiety 10%, of patients with cancer, compared with figures of 5% and 7% for past-year prevalence in the general population
- Poor recognition of depression and anxiety is associated with reduced quality of life and survival
- Some cancers, such as pancreatic and lung, can release chemicals that are thought to cause depression. Certain cancer treatments, such as chemotherapy and corticosteroids, are associated with depression. The psychosocial impact of a diagnosis of cancer can also be the cause of a mood disorder
- Depression in cancer patients receiving end-of-life care is no more prevalent than in patients living actively with cancer

#### **Box end**

Advances in cancer treatments mean that half of people now diagnosed with cancer can expect to survive for at least 10 years,<sup>1</sup> defining many cancers as long term conditions. Psychiatric illnesses such as depression and anxiety are common, but often neglected, complications of cancer, influencing quality of life, adherence to treatment, cancer survival, and treatment costs.<sup>2,3</sup> Depression and anxiety affect up to 20% and 10% of patients with cancer respectively, regardless of the point in the cancer trajectory, and whether in curative or palliative treatment.<sup>4</sup> Geographical variations in the diagnosis and treatment of depression or anxiety in cancer settings implies under-recognition of these problems.<sup>5</sup> Depression is

associated with poor adherence to cancer treatment and poor cancer survival,<sup>6</sup> and the increased risk of suicide in all patients with cancer<sup>7</sup> is a concern.

This clinical update outlines the prevalence, aetiology, and management of depression and anxiety in patients with cancer to raise awareness among doctors of the need to address the psychiatric consequences of cancer.

**Box start**

**Sources and selection criteria**

We conducted tumour-specific and treatment-specific PubMed searches, and used NICE guidelines, Food and Drug Administration data, and references known to us through our clinical and research work.

**Box end**

## **How common are depression and anxiety in patients with cancer?**

A systematic review and meta-analysis shows the prevalence of major depression (15%), minor depression (20%), and anxiety (10%) in patients treated for cancer.<sup>4</sup> These figures greatly exceed population estimates of past-year depression (5%) and anxiety (7%). Two thirds of patients with cancer and depression also have clinically significant anxiety symptoms.<sup>3</sup> Figures vary by cancer type, with major depression affecting an estimated 13% of patients with lung cancer, 11% of those with gynaecological cancers, 9% in breast cancer, 7% in colorectal cancer, and 6% in genitourinary cancers.<sup>8</sup> The highest levels of anxiety are reported in lung, gynaecological, and haematological cancers.<sup>9</sup> Evidence suggests these variations relate to the differing prognoses, pain levels, and degrees of body image disruption associated with each tumour type, as well as specific tumour-related neuropsychiatric effects and treatment-related neuropsychiatric side effects.<sup>3</sup>

Estimates of the prevalence of major depression in cancer patients greatly exceed the 2% reported for the general population.<sup>8</sup> However, 73% of these depressed cancer patients do not receive effective psychiatric treatment, and only 5% see a mental health professional.<sup>8</sup> Symptoms of anxiety in patients with cancer more often coexist with clinical depression than present as anxiety alone, and treatment for depression may also resolve anxiety.

## **Who is most at risk?**

Risk factors for depression and anxiety in cancer are poorly characterised. Those identified for depression in cancer include younger age and social deprivation, and (for colorectal and lung cancers) female gender.<sup>8</sup> Unlike in the general population, anxiety disorders in cancer are not associated with age, gender, or socioeconomic status.<sup>2</sup> They are associated with a history of anxiety or trauma,<sup>10</sup> and (for some cancers) with metastatic

disease.<sup>11</sup> Patients who exhibit a tendency to blame themselves for their cancer diagnosis are more likely to become depressed than those who consider other contributory factors.<sup>13</sup> Clinical practice also suggests that severity is influenced by factors such as functional limitations and poor social support.

In our experience patients with pre-existing psychiatric disorder require close vigilance after cancer diagnosis, as this may relapse or worsen at any point in the cancer journey. Examples include pelvic, breast, or rectal examinations re-traumatising patients with post-traumatic stress disorder, relapse of recurrent depressive disorder after mastectomy, and manic or depressive relapse of bipolar affective disorder due to essential treatment with corticosteroids.

Survival after a cancer diagnosis is reduced in people with pre-existing severe mental illness, even when accounting for delayed diagnosis, with mortality risk 90% higher in patients with schizophrenia and 20% higher in patients with prior depression<sup>12</sup>

## **What are the underlying causes?**

There are two main pathways by which depression and anxiety can arise in patients with cancer: the processes involved in the biopsychosocial model (with interdependent contributions of biological, psychological, and social factors) and the range of specific neuropsychiatric effects of certain cancers and their treatments. Cancer treatment may be an under-recognised yet reversible cause of severe (and sometimes rapid onset) illness.

### **Biopsychosocial causes**

Depression and anxiety in cancer most commonly arise from a patient's psychological reactions to diagnosis, treatment, relapse, end of life care, or survivorship.<sup>14</sup> Losses inherent to treatment (such as hair, sexual function, or organs), expectations regarding survival, and the effects on work and social roles can lead to protracted periods of psychological stress. The perception of illness can have physiological effects (such as sustained stress causing activation of the hypothalamo-pituitary-adrenal axis), giving rise to psychological symptoms that reach diagnostic thresholds for depression or anxiety.<sup>3</sup> The common physical side effects of conventional chemotherapies (such as vomiting, hair loss, mucositis, and peripheral neuropathy) can be a chronic psychological stressor.

Health anxiety describes a preoccupation with the fear of having a serious illness based on a misinterpretation of somatic symptoms. This may be understandable for patients in remission whose anxiety is reinforced by a past (and sometimes missed) cancer diagnosis

(see [fig 1](#)). Anxiety in patients with cancer is understood to reach pathological levels where it significantly impairs usual functioning, and is disproportionate to the level of threat.

**Fig 1.** Cognitive behavioural model of anxiety in the context of cancer

### **Direct neuropsychiatric effects of cancers or treatment**

No precise estimates are available for the proportion of depression or anxiety cases attributable to the direct biological effects of specific tumours or cancer treatments. Limited tumour-specific studies confirm that they represent a clinically significant minority.

#### *Site-specific cancers*

Several specific tumour types give rise to depression or anxiety (see infographic), most commonly tumours of the pancreas (severe cytokine-mediated depression) and lung (depressive and anxiety symptoms due to endocrine paraneoplastic syndromes).

About 70% of patients with pancreatic cancer experience depression, 50% have anxiety, and 30% experience both, with depression arising months before the cancer diagnosis and also late in the disease.<sup>15</sup> Levels of the cytokine interleukin-6, released by the tumour, are directly proportional to the severity of the depression.

Among patients with small cell lung cancer (SCLC), 15% will develop the syndrome of inappropriate antidiuretic hormone secretion (SIADH), of whom a large proportion would be expected to experience low mood driven by hyponatraemia.<sup>17</sup>

A third example is depression arising from malignant hypercalcaemia, which affects approximately 1% of UK cancer patients.<sup>19</sup> This is driven by ectopic parathormone-related peptide production in non-small cell lung cancer (NSCLC), myeloma, sarcoma, breast, renal, gynaecological, and head & neck cancers, but also arises from bone metastases in a range of tumours.

#### *Cancer treatments*

Corticosteroids can cause hypomania (often with psychotic features) at high doses and depression with longer-term low doses. Less well recognised by clinicians are the adverse neuropsychiatric effects of some conventional chemotherapeutic agents, hormone deprivation treatment, newer immunotherapies and targeted agents,<sup>20</sup> radiotherapy, and cancer surgery (see infographic and supplementary boxes 1-4 on [bmj.com](http://bmj.com)).

For example, in trials of androgen deprivation therapy for prostate cancer, men report statistically significantly higher rates of depression and anxiety throughout nine months of treatment than at baseline.<sup>21</sup>

Mood disorders (anxiety, euphoria, or depression) develop in 37% of patients with solid tumours who are treated with buparlisib; a small molecule targeted treatment..

Of patients who receive radiotherapy for head and neck cancer, 10% develop clinical hypothyroidism, of whom roughly two thirds would be expected to develop depressive symptoms.

After pelvic irradiation for gynaecological cancer, 14% of patients acquire vitamin B12 deficiency due to disrupted gut absorption, and here again depression is a common presenting complaint.

Bilateral oophorectomy in premenopausal women, whether as cancer prophylaxis or treatment, is associated with a long term increased risk of depressive disorder and of anxiety symptoms.

## **At which points in the cancer journey are patients affected by anxiety and depression?**

### **Pre-diagnosis**

Depression and anxiety may be the first sign of cancer for tumours exerting direct biologically-mediated effects on mood (see infographic).<sup>18</sup> This highlights the importance of excluding organic differentials when assessing all new psychiatric presentations. The incidence of cancer diagnosis in the first month after a first psychiatric presentation for anxiety is over triple that for the rest of the population, and particularly high in people over 65 years old.<sup>18</sup> Among patients aged over 50 years presenting to psychiatric services for the first time with depression, an estimated one in 54 will be diagnosed with cancer within a year; predominantly those cancers with neuropsychiatric effects.<sup>18</sup>

### **Diagnosis and treatment**

The estimated prevalence of depression is highest during the acute phase of cancer treatment.<sup>22</sup> Feelings of hopelessness as part of the syndrome of depression may influence refusal of cancer treatment. Up to 50% of women with breast cancer have a diagnosis of depression, anxiety, or both in the year after diagnosis, falling to 15% over five years.<sup>23</sup> Severe depression can sometimes present acutely during conventional chemotherapy, particularly for taxane-based chemotherapies, and post-chemotherapy depression may persist for up to 18 months.<sup>24</sup>

### **Discharge**

For some patients, an intense schedule of clinic, imaging, and treatment appointments delays their psychological adjustment to the cancer diagnosis until after treatment, which can

be understood as a protective form of denial.<sup>25</sup> Once the milestone of surgery or chemotherapy has passed, this may be the point at which a patient starts to consider the significance of a potentially life-threatening event and adjusts to long-term physical changes, at which point depression and/or anxiety may emerge (see patient's perspective box). Discharge from cancer services can represent a sudden cessation of regular support for some patients, and the perceived abandonment can increase levels of anxiety to diagnostic thresholds.

### **End of life**

Perhaps contrary to expectations, the estimated prevalences of depression (all types combined), and anxiety during end-of-life care (25% and 10% respectively) do not differ from those in non-palliative care settings.<sup>4</sup>

### **Survivorship**

Patients in remission from cancer beyond five years after diagnosis are termed cancer survivors, but they remain vulnerable to psychological distress as they adjust to this identity.<sup>14</sup> The prevalence of anxiety (18%), but not depression (12%), is significantly higher in cancer survivors than in healthy controls, persisting for up to 10 years.<sup>26</sup> Marked fear of recurrence is reported by 17% of long-term breast cancer survivors and is associated with depression and poor quality of life.<sup>27</sup>

## **What management approaches are recommended?**

*Address underlying causes*—Correct any direct biological causes (such as vitamin B12 deficiency, hypothyroidism, SIADH, or hypercalcaemia) and consider addressing other reversible causes (such as switching to another systemic anti-cancer treatment), at which point symptoms may resolve. Addressing perpetuating factors, such as pain, may also reduce the severity of depression.<sup>28</sup> When cessation of a specific anti-cancer treatment is not desirable because of a good tumour response, treat the mood symptoms as for any case of depression.<sup>28</sup>

*Stepped care*: Standard treatment guidelines apply to depression and anxiety in patients with cancer, but the following points highlight special considerations in cancer.

*Medication*: Choice of anti-anxiety or anti-depressant agent should be guided by clinical parameters, particularly interactions with chemotherapies and current or predicted bone marrow suppression, to identify specific contraindications (see “General prescribing pointers in patients with cancer” box in linked article). Among first line agents for depression and

anxiety, sertraline and citalopram generally have the least propensity for interactions and tend to be well tolerated.

*Psychological therapies:* Cognitive-behavioural formulations (see [fig 1](#)) can be a useful means of understanding the thoughts, feelings, and behaviours that can cause or maintain symptoms of depression or anxiety—such as in cases of treatment refusal, avoidance behaviour, or excessive reassurance seeking.

Availability of specialist psychological therapy for patients with cancer and comorbid depression or anxiety varies geographically. Major cancer centres in parts of the US, Australia, France, Germany, and UK sometimes offer integrated psychological support services (specialist counsellors and clinical psychologists embedded in cancer services). These deliver evidence-based therapies to individuals or groups, but they may not be available outside urban centres. Improving Access to Psychological Therapies (IAPT), the English programme for treating depression and anxiety, may be more accessible and also offers group or individual therapies, but services may lack specialist training in the complexities of working with cancer. Such expertise includes addressing adherence to treatment, complex illness beliefs, challenging side effects (including psychosexual), physical disfigurement, and end-of-life issues.

*Integrated Mental and Physical Cancer Care:* In a trialled system of collaborative screening and treatment, cancer clinical nurse specialists were supervised to deliver cognitive-behavioural interventions for depression, and GPs were guided by liaison psychiatrists to optimise the prescribing of antidepressant medication.<sup>29</sup> Based on evidence of this model's effectiveness in reducing depression and improving quality of life, the UK NHS Cancer Strategy suggests integrating multidisciplinary depression care into cancer care as a cost-effective means of addressing inadequate treatment and achieving parity of esteem for patients' mental and physical needs. Although long-term follow-up reveals no impact of this care model on survival, such collaborative care models are valued by patients for their impact on quality of life.

**Box start**

**Further reading**

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**Box end**

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**Box start**

**A patient's perspective**

I was diagnosed with triple negative breast cancer in late May 2011, undergoing a lumpectomy and re-excision, chemotherapy (FEC-T x 6) and radiotherapy. As I progressed through chemotherapy I felt very wobbly, scared that anxiety and depression were showing up again, something I had tried to deal with (with and without medication) since 2001. I stumbled across oncology counselling, and self-referred to local primary care mental health services for 16 sessions of cognitive behavioural therapy. My experiences have shown how vital it is that a range of psychological support is made available to fit the different types of challenges that cancer patients (and their carers) face. It is also essential that this support is made available within a specified timeframe, including beyond the end of treatment, when buried issues may often surface. This support needs to be made available in hospitals, linking with cancer teams and clinical nurse specialists to ensure everyone is aware such specialist support is available.

Caroline Carling, member of the Macmillan Mental Health and Cancer Taskforce

**Box end**

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**Box start**

**Education into practice**

- How does depression and anxiety differ in people with cancer? Does this article offer you ideas on how you might alter your practice around exploring psychiatric symptoms in cancer patients?
- Audit suggestion: How many of your patients have had their thyroid function checked in the first year after head and neck radiotherapy?
- Audit suggestion: Have all your patients who have had pelvic irradiation or gastrectomy had vitamin B12 estimations?
- Do you know what support services, for persistent physical consequences of cancer treatment or for psychological support, are available in your area for people living with and beyond a diagnosis of cancer?

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**Box end**

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**Box start**

**How patients were involved in the creation of this article**

We interviewed a range of our patients with cancer to find out what they felt were the important aspects to address in an article about psychiatric problems in cancer, and they mentioned the importance of highlighting that the nature of patients' distress changes as they transition through diagnosis, treatment, and post-treatment (for example when waiting for test results or living in fear of recurrence), and of being aware "that we may not be able to voice what's really going on for us, and (practitioners) may need to delve a little bit deeper to really help us".

We invited a patient representative to write a personal perspective on her experiences of depression in the context of cancer diagnosis and treatment and to review our article for its coverage of key points. She felt it was important to highlight how common mental health problems were both during and after cancer treatment, and the need for specialist psychological input.

**Box end**

Contributors: AP and AH conceived the article and conducted literature searches. AP drafted the article, with contributions from SS, NH, and AH. SS devised the cognitive behavioural model. All authors approved the final version of the article and agree to be accountable for all aspects of the work. AP is the guarantor.

Competing interests: We have read and understood BMJ policy on declaration of interests and have no relevant interests to declare. Our employers and Macmillan had no role in the preparation, review, or approval of the manuscript. The views expressed are those of the authors and not necessarily those of their employing trusts or of Macmillan.

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