

## Reactions of patients to the diagnosis and treatment of cancer

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More effective diagnosis and improved treatment have changed cancer from an inevitably fatal to an often curable disease. As a consequence, considerable care needs to be exercised in discussing both the diagnosis and treatment of the disease with the patient or, in the case of children, the parent. Initial reactions to learning that one has cancer include fear of death, disfigurement and disability; fear of abandonment and loss of independence; fear of disruption in relationships, role functioning, and financial standing; and denial, anxiety and anger. An important role of the physician is to recognise these fears and emotions and encourage the patient to share his or her thoughts. It is also important to provide necessary information both to correct misconceptions and to provide hope. Treatment-related concerns add a second source of distress to the patient and, if not optimally addressed, may prejudice the completion of effective treatment. Long courses of treatment may cause the patient to become much sicker symptomatically from the treatment than from the disease itself. Children, in particular, may be unable to tolerate treatment-related side effects. Especially demoralising for the patient are commonly used anti-cancer agents with high emetogenic potential. These include cisplatin, dacarbazine, streptozocin, actinomycin and nitrogen mustard. In many cases, patients suffer so badly from the symptoms of nausea and vomiting that they refuse further treatment. They describe cytotoxic, drug-induced nausea and vomiting as a nightmare. The recent introduction of a new class of anti-emetic agents, the 5-HT<sub>3</sub>-receptor antagonists, has improved patient quality of life during cytostatic treatment and, in some cases, permitted more aggressive therapy. Three 5-HT<sub>3</sub>-receptor antagonists are now widely used: Navoban® (tropisetron), Kytril® (granisetron) and Zofran® (ondansetron).

**Key words:** Navoban® (tropisetron), cancer, nausea, vomiting/emesis, anxiety, depression.

### Introduction

Cancer may be the most feared of all illnesses, being associated with death, pain and suffering. In recent years, advances in diagnosis and treatment have significantly improved the prognosis for many newly diagnosed patients. Indeed, for certain types of cancer the diagnosis is no longer synonymous with a death sentence. Unfortunately, the uncertainty that accompanies the knowledge that one has cancer – a potentially life-threatening illness – has a profound impact on an individual's outlook and state of mind. In addition, the very treatments that are life-saving, most notably radiation therapy and chemotherapy, are a source of considerable discomfort and distress. As noted in a recent *New England Journal of Medicine* article,<sup>1</sup> these regimens are 'better known for their toxicity than for their efficacy'. Patients are 'most fearful of the nausea and emesis caused by chemotherapy.' As a result of these two factors – the disease itself (and what it represents) and the trauma of treatment – there is ample cause for a wide range of emotional responses, including frank psychiatric disorder. In managing the care of patients, physicians should anticipate and recognise those stress factors that adversely influence quality of life. By taking measures to minimise the burden of these adverse stress factors, it is possible to enhance patient compliance and, in some instances, the actual success of anti-cancer treatment.

### Emotional/psychological responses to cancer

Fear of death is the most common, immediate and understandable response to being informed of a potentially life-threatening diagnosis. However, a number of other reactions invariably become evident. These include such concerns as loss of income and cost of treatment and thus financial status; physical disability and disfigurement; dependency on others; abandonment or disruptions in relationships; and

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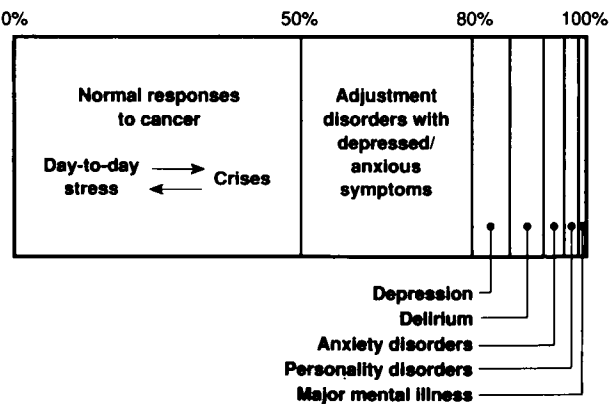
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diminished capacity for performing important roles in life.<sup>2</sup> Whether or not a person successfully negotiates and resolves these issues, and manages to maintain relatively normal activities and relationships, depends on many factors. Among these are the location, extent and nature of the cancer; the personality, coping style and mental health of the patient; and the presence or absence of financial and social supports.<sup>3</sup> Some patients respond to their illness by becoming highly focused and absorbed in researching information on their diagnosis and treatment, trying to achieve a sense of mastery and independence. Others become emotionally overwhelmed,<sup>4</sup> disorganised or paralysed, attempting to avoid thinking about or dealing with their new reality. In addition to these cognitive responses, patients may also manifest somatic changes, such as increased physical symptoms, loss of appetite and sleep difficulties, and psychiatric symptoms, such as depression, anger and emotional numbness.<sup>3</sup>

Surprisingly, most cancer patients do not develop a major psychiatric disorder. A large study<sup>5</sup> found that 50% of patients experience transient 'adjustment reactions' in response to the stress factors of their illness. About 30% of patients develop time-limited anxiety or depression or both. Only 20% of patients develop serious anxiety, depression or other mental disorder (Figure 1).

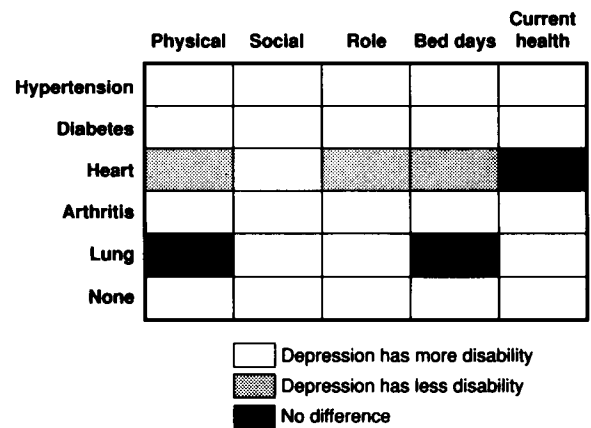


**Figure 1.** Spectrum of psychiatric disorders in cancer. Adapted from Derogatis *et al.* *JAMA* 1993; 249: 751-757.

Another well-established relationship between psychiatric symptoms and cancer involves the degree of physical disability and discomfort. The relationship between physical symptoms, physical functioning and mental health has been demonstrated in patients with many types of disorder. Noyes and his co-workers<sup>6</sup> studied a cohort of cancer patients and observed the following: physical manifestations of

cancer are the greatest overall sources of distress; aggregate symptoms are strongly associated with physical functioning and mental health; and psychiatric symptoms are generally proportional to somatic symptoms. Loss of life's meaning, including thoughts related to death, were actually found to be a comparatively minor source of distress. The authors commented that somatic manifestations of disease are more immediate and more palpable than fear of death and that threat of death is something patients come to terms with after an initial shock.

A survey of nearly 25,000 medical and mental health outpatients examined the functioning and sense of well-being of those with common chronic disorders. These included hypertension, diabetes, heart disease, arthritis, lung disease and depression (Figure 2).



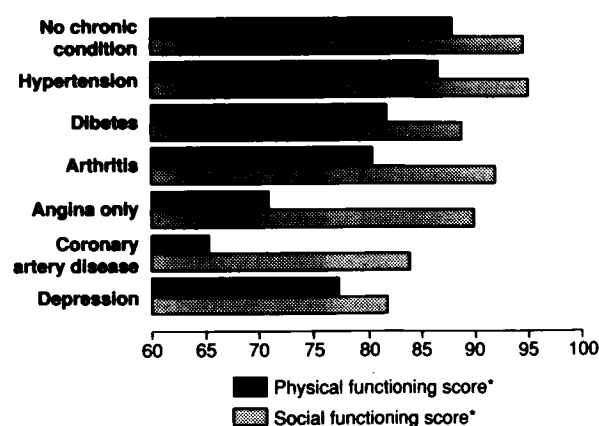
**Figure 2.** Effect of depression on functional disability in chronic medical conditions. Wells *et al.* *JAMA* 1989; 262: 914.

Among the measures of disability and daily functioning were physical limitations, social role, occupational functioning, days spent in bed, and subjective estimate of health. It was found that depressed patients rated worst on all measures, except for physical and social functioning where only patients with angina and coronary artery disease exhibited greater disability (Figure 3).<sup>7</sup>

An ever-present risk in depressed patients is suicide. Breitbart<sup>8</sup> has described factors that predispose to suicide in cancer patients. Vulnerability for suicide included depression and feelings of hopelessness and poorly controlled pain and symptom burden.

### Side effects resulting from treatment

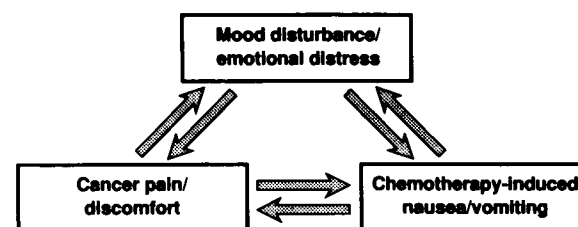
Adding to the misery experienced by cancer patients are side effects of anti-cancer treatment. In addition to



**Figure 3.** Physical and social functioning in depression and chronic illness. \* A score of 100 = perfect functioning. Wells *et al.* JAMA 1989; 262: 914.

fatigue, nausea and vomiting probably represent the most commonly reported side effect in patients undergoing chemotherapy. Gebbia<sup>9</sup> has observed that intense nausea and vomiting 'may be considered one of the major causes of physical and psychological distress for patients with cancer and one of the leading reasons of refusal of otherwise successful medical treatment'. Physical complications of nausea and vomiting include dehydration, electrolyte disturbances, Mallory-Weiss syndrome, reduction in food intake, and aspiration-related respiratory disease. It is common for patients to develop severe adverse conditioned responses to chemotherapy. For example, anticipatory nausea and vomiting may develop after the initial period of chemotherapy, so that nausea and vomiting occur spontaneously hours or days before the next series of treatments. There may also be conditioned response when the patient is exposed to sights and smells reminiscent of the chemotherapy experience. Even six months after treatment, two-thirds of patients report nausea, while 5% experience nausea in response to specific stimuli. Anxiety is also common. Pre-existing anxiety has been identified as a predisposing factor for the development of nausea<sup>3</sup> (Figure 4). The importance of antiemetic control in the chemotherapy-naïve patient has been underscored by Borison,<sup>10</sup> who has observed:

'When emesis has been poorly controlled during past courses of chemotherapy, a patient is predisposed to unsatisfactory antiemetic results with subsequent similar chemotherapy. In one trial, in which patients received their initial treatment with the same antiemetic, it was noted that major control was three times more likely in those who had no previous chemotherapy.'



**Figure 4.** Relationship between emotional state and symptom burden.

Rees<sup>11</sup> has observed that better control of nausea and vomiting can indeed increase the likelihood of patients being offered chemotherapy. He estimates that the risk of these side effects may account for 30% of patients with certain tumours not being offered chemotherapy.

Thus, the consequences of drug-induced nausea and vomiting can include not only suffering and pain, but intolerance of further treatment to the point where optimal doses cannot be administered or where there is refusal of further anti-cancer treatment.<sup>12</sup>

Many chemotherapy patients develop symptoms that resemble post-traumatic stress disorder.

### Prevention of nausea and vomiting

Until very recently, nausea and vomiting were considered unavoidable side effects of cancer chemotherapy.<sup>12</sup> Although many types of antiemetic drugs have long been available (e.g. phenothiazines, butyrophenones, substituted benzamides, corticosteroids, anticholinergic drugs, cannabinoids and antihistamines), these compounds rarely achieved complete control of the side effects, and produced considerable adverse effects themselves (Table 1).

Serotonin antagonists represent the newest and most effective of the antiemetic agents. The older drugs are all either of limited therapeutic value or produce serious adverse effects. For example, the commonly-used dopamine D<sub>2</sub>-antagonist drugs (e.g. metoclopramide, haloperidol and prochlorperazine) frequently produce akathisia, dystonia, parkinsonism and depression. In the past, chemotherapy remained an unpleasant experience in spite of and, in some cases, because of these drugs.

The serotonin 5HT<sub>3</sub>-antagonists Navoban® (tropisetron), Zofran® (ondansetron) and Kytril® (granisetron) provide both enhanced efficacy and fewer adverse effects. A drug like Navoban® can be given once a day and administered as monotherapy,<sup>13</sup> thus reducing the total burden of procedures for the

**Table 1.** Emetic potential of drugs used to treat patients with cancer

Highly emetogenic drugs	Moderately emetogenic drugs	Mildly emetogenic drugs
Cisplatin	Cyclophosphamide	Fluorouracil
Mechlorethamine hydrochloride (nitrogen mustard)	Doxorubicin	Methotrexate
Streptozocin	Carboplatin	Etoposide
Dacarbazine	Mitomycin	Vincristine
Carmustine	Asparaginase	Bleomycin
Dactinomycin	Azacitidine	

Alastair *et al.* *New Eng Med J* 1993; **329**: 1790–1796.

patient, and minimising the risk of side effects. The absence of extrapyramidal side effects, such as acute dystonic reactions and akathisia, is particularly important for children and young adult patients,<sup>14</sup> who are most vulnerable to these reactions with the dopamine antagonists. The potential benefits of serotonin antagonists, when used alone or in combination with other compounds, are significant. They include: improved quality of life during chemotherapy, as reflected by lower incidence of side effects and emotional distress; greater likelihood of complete control over nausea and vomiting, with subsequently reduced risk of the development of anticipatory symptoms; improved compliance with chemotherapy; potential for more aggressive, and hence more effective, chemotherapy regimens; and higher rate of 'elective' chemotherapy. The last point is increasingly important in the context of improved methods of cancer detection. Early screening techniques are enabling physicians to find cancers in their earliest stages, sometimes years before they might produce physical signs and symptoms. Since there may not always be a consensus on the real benefits of treating these early stages of the disease, the side effects of the treatment might be the determining factor in making a decision. The ability to block nausea and vomiting might thus lower the threshold at which patients will proceed with chemotherapy.

### Cancer in children

Although cancer is less prevalent in children than in adults, a larger percentage of childhood cancers, such as leukaemia, lymphoma, and central nervous system tumours, are responsive to radiation therapy and chemotherapy. It is estimated that the total of childhood cancer survivors in the United States is about 150,000,<sup>15</sup> a reflection of the efficacy of treatment. But there is a price for this success. The therapy regimens,

which tend to be aggressive and long, often produce both acute and long-term medical, neurological and psychiatric impairment. For example, emesis and nausea in children are of special concern because of the dangers associated with appetite loss and disturbances in nutritional and electrolyte balances.<sup>16</sup> Long-term complications, such as conditioned responses, or flashbacks, as seen in post-traumatic stress disorder, are more common in children than in adults. It is therefore not surprising that, as a recent article<sup>17</sup> has noted, the improved outcomes for childhood cancer survivors and their families are demanding that there be improved recognition and management of quality-of-life issues.

The management of disease symptoms and treatment-related side effects must take into account several facts. First, children are more susceptible to chemotherapy-induced nausea and vomiting.<sup>1</sup> Secondly, children are less able to express suffering and are thus more likely to be under-medicated for pain. Thirdly, there is a general antipathy on the part of carers toward use of opiates in children, a fact that also contributes to inadequate analgesia.

In the case of children, optimal management of stressful and painful procedures is important not only for current comfort, but also for long-term adaptation. Haase and Rostad<sup>17</sup> offer experiences of children completing cancer therapy. They describe what they term 'cascading fears', where concerns about relapse are not limited to the fear of the cancer returning. 'The children's fears focused more on having to receive chemotherapy again and experiencing its awful side effects.' The children, especially the older ones, experienced their fears in a domino-like way. '... Interestingly, no-one mentioned any thoughts or fears of dying should the cancer recur, but the thought of actively going through treatment again was expressed as unthinkable. The children dreaded going through the experience a second time more than having had cancer in the first place.'

The incidence of post-traumatic stress disorder-like symptoms appears to be higher in children,<sup>3</sup> in part as an outgrowth of the reactions to chemotherapy, but also because of the associated painful, invasive procedures, such as repeated venipunctures.

## Conclusion

The diagnosis of cancer is emotionally overwhelming, if not catastrophic, and associated with psychiatric morbidity. Many factors influence the degree to which pathological anxiety, depression or other psychiatric disturbances develop. Proper control of pain and other symptoms is associated with a better emotional state. Side effects resulting from treatment are a major cause of physical and psychological distress, often proving more disabling than the illness itself. Prevention of drug-induced nausea and vomiting is associated with improved mental status, better compliance and reduced long-term emotional trauma. It is particularly important to provide optimal control in chemotherapy-naïve patients, in order to prevent the development of adverse, conditioned responses, such as anticipatory emesis and phobias.

The objectives for cancer patient management thus include: (1) cure, through radiation, surgery or chemotherapy; (2) symptom relief, through palliative procedures or analgesia; (3) reduction of treatment-related side effects, through use of steroids, dopamine D<sub>2</sub>-antagonists or serotonin 5HT<sub>3</sub>-antagonists.

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