Management of mood disorders in patients with advanced illnesses

Hospital doctors often assume that patients with advanced life-limiting illnesses will be depressed and that as depression is understandable treatment is not indicated. However, differentiating natural sadness from major depression has important therapeutic implications.

Mood disorders are common in patients with advanced illness. The exact prevalence depends on how the mood disorder is identified, the diagnostic criteria used and how close the patient is to death. A systematic review of prevalence studies showed that approximately 15% of patients with advanced disease will have a major depressive disorder based on psychiatric interview (Hotopf et al, 2002). Senior hospice doctors and clinical nurse specialists in palliative care who work exclusively with patients with advanced disease feel they lack training and confidence in diagnosing and managing depression, have difficulty discussing low mood with patients and find differentiating depression from 'natural sadness' difficult (Lloyd-Williams and Payne, 2003; Lawrie et al, 2004). It is, therefore, not surprising that hospital doctors who see patients with advanced disease less frequently find the diagnosis and management of mood disorders difficult.

Sadness

Sadness is a normal emotional reaction to loss, and is commonly experienced by patients with advanced life-limiting illness associated with loss: loss of physical function, loss of role and, ultimately, loss of life. Sadness may oscillate with other emotions, such as anger and fear, and usually resolves over a number of weeks, but can recur at times of further physical deterioration. Sadness varies from day to day, within the day, and while it may lead to temporary withdrawal does not lead to marked functional impairment.

Major depressive disorder

Patients with a major depressive disorder have disabling symptoms, both psychological and physical. The diagnostic criteria for major depressive disorder are that a person has either abnormally depressed mood or abnormal loss of interest and pleasure, or both, nearly every day for at least 2 weeks. The low mood should significantly interfere with the person's life and at least five of seven possible additional symptoms (*Table 1*) should be present during the same 2-week period (World Health Organization, 1992). The symptoms should not be the result of a psychosis, physical illness, alcohol, prescribed or illicit medication, or a 'normal' bereavement. Hence, diagnosing a major depressive disorder in a patient with an advanced physical illness is intrinsically difficult as many of the physical symptoms of the illness will overlap with the symptoms of depression: fatigue, weight loss, reduced appetite and slowing of activities.

Different ways of overcoming this difficulty have been suggested to prevent an over-diagnosis of depression. Endicott (1984) proposed that the symptoms in italics in *Table 1* are substituted by: fearfulness or depressed appearance, social withdrawal or decreased talkativeness, brooding, self-pity or pessimism, and cannot be cheered up, does not smile, no response to good news or funny situations. Chochinov et al (1994) suggested that in patients with cancer the additional symptoms are less important than the presence nearly everyday for at least 2 weeks of abnormally depressed mood or loss of interest or pleasure, However, there may still be diagnostic difficulties as many patients with advanced physical illnesses will lose interest in activities that they previously enjoyed as they no longer have the physical ability to engage in them. Generally patients with depression will no longer

Table 1. Additional symptoms: at least five are required for the diagnosis of a major depressive disorder

Abnormal weight loss (when not dieting) or decrease in appetite or abnormal weight gain or increase in appetite
Abnormal insomnia or abnormal hypersomnia
Abnormal agitation or abnormal slowing (observable by others)
Abnormal fatigue or loss of energy
Abnormal self-reproach or inappropriate guilt
Abnormal poor concentration or indecisiveness
Abnormal morbid thoughts of death (not just fear of dying) or suicide

Endicott (1984) suggested symptoms in italics could be substituted – see text.

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gain pleasure or take interest in any activities, even activities that they could enjoy despite their lack of physical ability such as watching sport on television or talking with friends, while patients with physical fatigue will still enjoy more sedentary activities.

Adjustment disorder

Some patients may exhibit low mood that persists for many weeks, beyond what would be expected of 'natural' sadness, but which is not sufficiently severe to fulfil the diagnostic criteria for major depression, although it does interfere with their daily routine. They may also complain of worry and a feeling of inability to cope with their present situation or plan ahead. Such patients may have an adjustment disorder (*Figure 1*) (World Health Organization, 1992). In some groups of patients, such as those recently diagnosed with cancer, adjustment disorder is more common than major depressive disorder (Derogatis et al, 1983). How the diagnosis of adjustment disorder is made is debated within psychiatry, but it is essentially a diagnosis of exclusion (Strain and Diefenbacher, 2008).

Other differential diagnoses

It should not be assumed that a patient who sits quietly on the ward with reduced facial expressiveness, motor or speech retardation and somnolence is depressed, unless an assessment has been undertaken to ensure that he/she does not have symptoms suggestive of a hypoactive delirium, such as impairment of consciousness or attention, memory impairment, disorientation, hallucinations, illusions and sleep–wake cycle disturbance (Casarett and Inouye, 2001). A patient with excessive anxiety, especially one who has not previously suffered from nervousness or been a 'worrier' in the past, may have an underlying depressive disorder.

Although the true incidence of suicide in patients with advanced disease is unknown it is believed to be rare (Grzybowska and Finlay, 1997). It is higher in patients with delirium or depression and it is important to elicit if a patient has had suicidal thoughts. There is no evidence that raising the issue will increase the likelihood of suicide.

Screening

Given the diagnostic difficulties it is not surprising that many patients with physical illness do not have their mood disorders identified or treated (Maguire, 2000). The National Institute for Clinical Excellence (NICE) (2004) recommends that all patients with advanced disease should 'be systematically screened for psychological problems at key points in the patient pathway' and many screening instruments have been validated for use in palliative care patients with a range of illnesses (Lloyd-Williams et al, 2003). However, doubt has been cast on whether routine screening for depression outside of psychiatric settings improves psychosocial outcome (Gilbody et al, 2001) and physicians are reluctant to use even short screening instruments that take less than 2 minutes to complete (Mitchell et al, 2008). Although screening may ensure patients' psychological symptoms are assessed many palliative care patients are too fatigued or confused to complete them (Ward et al, 2004).

The Hospital Anxiety and Depression Scale has moderate sensitivity and specificity in palliative care patients and is therefore of limited use, but the very specific single question 'have you felt depressed most of the day, nearly every day, for 2 or more weeks?' is both diagnostically sensitive and specific (Lloyd-Williams et al, 2003). There are a number of 'red flags' that might alert a doctor to a patient having a mood disorder (*Table 2*).

Figure 1. Definition of an adjustment disorder. From World Health Organization (1992).

> A state of subjective distress and emotional disturbance, usually interfering with social functioning and performance, and arising in a period of adaptation to a significant life change, or to the consequences of a stressful life event, including the presence or possibility of serious physical illness. The onset is usually within 1 month of the occurrence of the stressful event or life change, and the duration of symptoms does not usually exceed 6 months.

Management

Differentiating sadness from adjustment disorder and depression is important as each requires different management. If patients are expressing a risk of harm to self or others referral to specialist psychiatry services should be arranged. Other reasons for referral to psychiatric services identified by Block (2000) are uncertainty about the diagnosis, psychosis, unresponsiveness to therapy with first-line antidepressants and requests for assisted suicide.

Sadness

Allowing patients time to express their concerns and feelings, especially when given bad news, has been shown to be beneficial and prevent later anxiety and depression (Block, 2000). Some explanation as to the feelings they may experience is important as is regular contact with professionals.

Adjustment disorder

The primary treatments for adjustment disorder are the 'talking therapies' including counselling, psychotherapy and support groups. The aims of treatment are to accelerate

Table 2. Red flags for mood disorders

Sad facial expression
Sudden change in function with no obvious cause
Excessive anxiety
Death wish or request for physician-assisted suicide
The patient makes you feel depressed or despondent

the natural adjustment process, enhance individual coping strategies and prevent maladaptive solutions. Patients may benefit from support groups and talking to patients with similar experiences. A small number of patients may also require medication such as benzodiazepines or antidepressants (Strain and Diefenbacher, 2008).

Depression

Trials have demonstrated the effectiveness of both psychological interventions and pharmacological interventions at relieving distress and improving quality of life (Block, 2000). No controlled trials have compared the efficacy of combined interventions, but most professionals recommend a combined approach using psychotherapy, education and antidepressants. Treatment choice should reflect individual patient preference including past experiences, outcome of previous interventions, prognosis and ability to engage with psychological therapies.

Psychological

Structured psychological interventions have been found to be effective for moderate to severe depression and are generally preferred to medication by patients (Timonen and Liukkonen, 2008). Unfortunately these treatments are not readily available in all areas and many patients with advanced illness will not have sufficient energy or time to engage with them.

Pharmacological

Given that patients with advanced illness may have a prognosis of only weeks or months doctors are often reluctant to start treatment for depression, concerned that they may burden patients with medication-related side effects and that patients will not live long enough to gain the benefits (Lawrie et al, 2004; Maguire, 2000). However, doctors are generally poor at predicting prognoses (Christakis and Lamont, 2000) and a meta-analysis of selective serotonin-reuptake inhibitors (SSRIs) suggested a therapeutic response in the first week of treatment (Tylee and Walters, 2007). Therefore even patients estimated to be within their last few weeks of life may still benefit from treatment with an antidepressant, and patients should not be denied potentially effective treatments that can enhance their quality of life based on estimated prognosis alone.

There are too few trials of antidepressants in patients with advanced illness to draw conclusions about the best drug to treat depression in this group (Ly et al, 2002). There are, however, studies of antidepressants in patients with a range of physical illnesses and a systematic review of these by Gill and Hatcher (1999) showed that antidepressants result in significant improvements in patients with depression more frequently than either placebo or no treatment.

When prescribing antidepressants the possible side effects and any interactions with other drugs need to be considered, along with patient preference, experience with previous medications and other symptoms. The choice of antidepressants is either tricyclics, SSRIs, one of the newer generation antidepressants, or psychostimulants. The systematic review of antidepressants in patients with a coexisting physical illness showed a trend towards tricyclics being more effective than SSRIs, but patients in this group were more likely to drop out as a result of side effects (Gill and Hatcher, 1990). SSRIs are the most frequently used antidepressant medication in palliative care (Lawrie et al, 2004), which is not surprising as the side effects of tricylics are not well tolerated by patients with advanced illness; these include drowsiness, dry mouth, constipation, urinary retention, hypotension and arrhythmia.

The authors' treatment recommendations for patients with advanced illness are shown in *Table 3*. Citalopram and mirtazapine are effective with a favourable side-effect profile and have a low incidence of drug interactions. Mirtazapine can be useful in patients who experience nausea or when a sedative or anxiolytic effect may be beneficial and there is some evidence to suggest it may act more quickly than other preparations (Fawcett and Barkin, 1998). Both mirtazapine and citalopram have the additional advantage of being available in liquid form for patients unable to swallow tablets.

Table 3. Treatment recommendations

Drug	Preparations	Dose range	Important points
Citalopram	10, 20, 40 mg tablets 40 mg/ml oral drops	20–60 mg daily	Start at a lower dose in elderly and titrate Caution in severe renal impairment Favourable side-effect profile Low risk for drug interactions Liquid preparation available
Mirtazapine	30 mg tablets 15 mg, 30 mg, 45 mg orodispersible tablets 15 mg/ml oral solution	15–45 mg daily (one or two doses)	Caution in severe hepatic and renal impairment Rare risk of causing neutropenia and agranulocytosis Favourable side-effect profile in patients with advanced illnesses (increased appetite, weight gain, and sedation at lower doses) Some evidence of more rapid onset of action Low incidence of interaction with other drugs Safe and effective in the elderly, and in patients with a history of seizures, cardiac failure or diabetes

Psychostimulants

Although less commonly used to treat depression in palliative care patients in the UK, psychostimulants should be considered in patients with a limited life expectancy in whom a rapid response is required, for example when depression severely interferes with decision-making capacity. In addition to improving opioid-induced sedation and fatigue, studies have shown improvements with psychos-

timulants in the symptoms of depression in patients with a range of co-existing medical problems including cancer, AIDS, and neurological disease; up to two thirds of patients benefited, with improvement seen after only 2 days (Homsi et al, 2000). The use of methylphenidate for treatment of depression is beyond the drug licence; it is generally well tolerated but should be used with caution in patients with cardiovascular disease and be given in divided doses before midday (starting dose 5 mg once daily titrating to 30 mg daily). Side effects such as anxiety and motor restlessness reverse quickly on discontinuation.

Conclusions

'Natural' sadness differs from adjustment disorder and major depressive disorder; although the distinction in patients with advanced illness can be difficult it has important therapeutic implications. Patients with major depressive disorder should be treated with antidepressants such as citalopram or mirtazapine. **BJHM**

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KEY POINTS

- Mood disorders are common in patients with advanced life-limiting illnesses.
- Differentiating sadness, adjustment disorder and major depression is important but can be difficult.
- Effective treatment requires pharmacological and non-pharmacological interventions.
- Patients with major depressive disorder require treatment with antidepressants such as citalopram and mirtazapine.
- Patients who do not respond to treatment, request physician-assisted suicide, or have suicidal ideas should be referred to mental health services.