Depression and physical illness

Summary

- Depressive symptoms frequently accompany physical illness, but the association between the two is complex. The combination has detrimental implications for the patient's health outcome, quality of life, medical treatment and health care use.
- The presence of physical symptoms of the medical illness can lead to challenges in recognising and diagnosing depression. This is best dealt with by placing greater emphasis on the psychological symptoms of depression.
- Recognition may be improved through use of appropriate screening tools for depression in medically ill patients.
- The management of depression in the setting of medical illness involves both general and specific approaches. General approaches include optimal treatment of the medical illness, exclusion of treatments that are associated with depressive symptoms, and simple general health strategies aimed at improving sleep and exercise.
- Good evidence exists for selective psychotherapeutic approaches and antidepressant treatments, but care is required to avoid drug–drug and illness–drug interactions with the latter.

Depressive symptoms frequently accompany physical illness, but the association between the two is complex. Medically ill patients with depression have reductions in quality of life,[1,2] increased medical morbidity and mortality,[3] increased functional disability,[4,5] reduced occupational performance,[4] and reductions in role functioning. Other implications of depressive comorbidity include prolonged hospital admission, amplification of physical symptoms,[6,7] reduction in adherence to medical treatment,[8] and increased medical costs and health care use.[9,10] Here, we focus on recognition, diagnosis and management of comorbid depression in patients with medical illness.

Epidemiology

It has been estimated that rates of depression rise from 2%–5% in the community to 5%–10% in primary care settings and 6%–14% in hospital inpatients.[11] Reported rates of depression vary considerably between individual medical illnesses (Box 1). High rates of depression have been noted in patients with neurological disorders, particularly epilepsy (20%–55%), multiple sclerosis (40%–60%) and stroke (14%–19%). There is also considerable variability of reported rates of depression within individual medical illnesses. For example, reported rates of depression in patients with idiopathic Parkinson disease (IPD) vary from 2.7% to 90%.[17] Demonstrating more realistic estimates, a systematic review found that 17% of patients with IPD had major depression, 22% had minor depression and 13% had dysthymia.[18]

Recognition and diagnosis

Depression in physically ill patients presents challenges in recognition and diagnosis. One reason for this is the difficulty in accounting for physical symptoms. Depressive symptoms are often clustered into biological (somatic), psychological and social symptoms (Box 2). Many diagnostic tools and scales for depression rely heavily on the presence of somatic symptoms, including insomnia, loss of appetite, anergia and reduced libido, to confirm a diagnosis. However, the somatic symptoms associated with depression are frequently also present in many physical illnesses, causing uncertainty about their attribution to either depression or the physical illness. In a similar way, social symptoms of depression, including withdrawal and impairments in role functioning, may occur in both depression and physical illness, making them unreliable as markers of depression in medically ill patients. The diagnosis of depression in medically ill patients therefore relies more heavily on symptoms of psychological distress, including preoccupation with guilty themes and failure, impairments in self-esteem, and an inability to derive joy from previously enjoyed activities.[19]

A second issue reducing recognition of depression in physically ill patients is the uncertainty surrounding the extent of symptoms. Physical illness is inevitably associated with losses, and depressive symptoms such as sadness, worry and irritability may be judged by both patients and primary carers as an "understandable" reaction to these losses, and subsequently minimised in importance. This kind of misjudgement by the clinician can lead to either underdiagnosis of depression or overdiagnosis and inappropriate prescribing of antidepressants, adding to the side-effect load of other medications.

Several depression rating scales have been used as screening tools to enhance the recognition of depression in medically ill patients. The Center for Epidemiologic Studies Depression Scale (CES-D) is a 20-item self-report measure that takes around 5 minutes to complete and includes only four somatic items. Good sensitivity and specificity in medically ill populations have been reported with cut-off

1 Prevalence of depression in medical illnesses

Medical illness and reference	Prevalence of depression
Cancer[12]	0–38%
Cardiovascular disease[13]	17%–27%
Chronic obstructive pulmonary disease[1]	20%–50%
Stroke[14]	14%–19%
Diabetes[15]	9%–26%
Epilepsy[16]	20%–55%
Idiopathic Parkinson disease[17]	2.7%–90%

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2 Clustering of depressive symptoms

Biological	Psychological	Social
Insomnia	Loss of interest or pleasure	Social withdrawal
Poor appetite	Worthlessness	Difficulties in relationships
Weight loss or gain	Hopelessness or helplessness	Reduced leisure activities
Loss of energy	Preoccupation with death	Difficulties at work
Loss of libido	Guilt or failure	Impaired role functioning
Poor concentration	Illness as punishment	

scores of 16–17;[20] however, low positive predictive value (PPV) limits its use as a screening instrument for depression. The Hospital Anxiety and Depression Scale (HADS) is a 14-item self-report scale from which an anxiety score and a depression score can be derived. It was developed specifically for measuring depressive symptomatology in medically ill populations.[21] The depression subscale is based on self-reported anhedonia (the inability to derive enjoyment). The HADS has similar reported psychometric properties to the CES-D and also takes only 5 minutes to complete. The latent structure of the HADS has recently been questioned, and it may be best understood as a reliable general measure of distress in medically ill patients.[22] The nine-item self-report Patient History Questionnaire (PHQ-9) was originally developed as the initial screening tool of the PRIME-MD (Primary Care Evaluation of Mental Disorders), a diagnostic instrument for anxiety, depression and eating disorders in primary care.[23] The PHQ-9 has been trialled in large populations of medically ill patients, with good sensitivity, specificity and PPV. The Beck Depression Inventory (BDI) has been extensively used as a screening tool for depression, but it is lengthy (taking 10–15 minutes to complete) and includes a number of somatic items, making it less helpful for use in medically ill patients.[24]

Other very brief screening tools for depression in medically ill populations have been developed, including "the distress thermometer" (see Couper et al, *page 13*),[25,26] single-item questions such as "Are you depressed?" or "Do you often feel sad or depressed?", and the two-item version (PHQ-2) of the PHQ-9 that asks the patient for a self-report regarding loss of interest or pleasure and feeling "down, depressed or hopeless". The brief single-item tools are limited by reports of lower sensitivity, specificity and PPV, although the PHQ-2 shows promise. Unfortunately, few of the abovementioned screening tools (apart from the CES-D) have been validated against the most important standard, which is a psychiatric interview and associated clinical diagnosis.

Management

General management approaches

The treatment of depressive comorbidity with medical illness involves both general and specific approaches. While it may appear obvious, it is important to maximise the management of the medical illness, which requires liaison with other clinicians involved in the patient's care. Strategies include a re-examination of the illness and a thorough review of the treatments provided so far, including a review of the success or otherwise of treatments, and their side effects. Any medical treatments not found to be helpful should be ceased, as they are likely to simply add to the patient's side-effect burden, which can contribute to anergia, poor concentration, sleep difficulties or impairments in general functioning. A rehabilitation approach should be considered for chronic conditions, as a state of deconditioning may contribute to fatigue and loss of functioning, which tends to reinforce negative views of the self, lower self-esteem and confidence, and may contribute to maintaining a "sick role". Rehabilitation approaches need not be inpatient programs but rely on an individual reassessment of the disorder and its management, the setting of goals and review of those goals after a predetermined period of time.

A detailed review should be made of medications prescribed for the medical disorder, to exclude agents that have been associated with depressive symptoms. While many medications carry warnings regarding the potential for changes in mood, these are largely based on case reports of variable critical rigour, and there are few targeted trials of sufficient methodology to accurately identify the risk of emergent depressive symptoms. There is good evidence linking atypical depressive syndromes with corticosteroids, interferon-α, interleukin-2, gonadotropin-releasing hormone agonists, mefloquine, propranolol and some antiepileptic medications, including topiramate.[27]

Some simple interventions should be offered to all patients with comorbid depression and physical illness. As sleep is frequently impaired, basic sleep-hygiene techniques should be suggested. Patients with a physical illness have often been subjected to a period of rest. Although this may be necessary during the acute phase of the illness or in the postoperative phase, deconditioning (with associated lethargy and low mood) can occur rapidly. A structured physical activity program tailored to the individual's capacity can be beneficial for both the medical and emotional problems of the patient.[28] Ideally, this can occur two or three times per week for up to 1 hour, depending on the patient's physical reserve, and can be undertaken individually, with a family member or, preferably, in a group with other patients with similar physical problems. Peer support programs developed to help both patients and carers are often available through non-government organisations. Such programs can help with information and practical support options and, most importantly, they can provide support groups where patients and carers can share experiences, support each other, and derive hope from seeing others successfully coping with their illness.

Medical conditions can be chronic, leading to gradual readjustments of family dynamics and interpersonal relationships. Patients may have relinquished important roles within the family, at times making them feel less valued and more helpless and dependent. The added burden on other family members may increase stress and occasionally resentment within the family unit, particularly if the illness is not well understood by family members. The development of depressive symptoms may be a good opportunity for clinicians to re-examine family relationships, provide explanations and prognoses, and to understand support systems within the family. This can

help the patient feel supported and also engage the family in a proactive approach to maximising functioning, fostering independence of the patient, and returning critical roles back to the patient to help improve his or her sense of meaning and purpose.

Specific management approaches

Specific management approaches include those used in other forms of depression, but with modifications depending on the stage of the illness, the degree of the symptoms, the potential side effects of the treatment, and the interaction with the underlying medical disorder. These approaches include psychotherapeutic treatments, pharmacological management and, rarely, more invasive treatments such as electroconvulsive therapy.

Psychotherapeutic interventions

Psychotherapeutic management of depressive symptoms in people with medical illness depends on the severity of the symptoms, the nature of the medical disorder and the degree to which the patient will engage in the treatment. Patients with issues such as significant cognitive impairment, communication problems (eg, dysarthria, tracheostomy) or mobility problems may present challenges in providing intensive psychotherapeutic interventions, but many patients can benefit from less intensive programs (including group exercise and peer support programs).

For patients with mild to moderate depressive symptoms, several psychotherapeutic interventions have been shown to be of benefit. Many psychotherapy trials conducted in medically ill populations involve patients with cancer. From these trials, there is good evidence for the effectiveness of cognitive behaviour therapy (CBT), which can be delivered in group or individual formats. A recent meta-analysis of randomised CBT trials involved somatically ill patients, including those with multiple sclerosis, cancer, HIV infections, heart disease and chronic obstructive pulmonary disease, who had a depressive disorder or depressive symptoms. Overall, the effect size of the improvement in patients treated with CBT was −0.49, with greater effect sizes in those with a depressive disorder (−0.83) compared with those with depressive symptoms (−0.16).[29] The authors concluded that CBT significantly reduced depressive symptoms in patients with somatic disease but, where comparisons were made with other psychotherapies (mainly supportive-expressive psychotherapy), there was little difference between the groups, raising the possibility that non-specific therapeutic effects may be present.

In patients with diabetes mellitus, several psychotherapeutic interventions, including CBT, relaxation training and supportive psychotherapy, have been shown to reduce depressive symptoms.[30] Several studies have compared "counselling" with CBT approaches in patients with cancer, cardiovascular disease or multiple sclerosis, with no differences in efficacy between the two.[31] Supportive group programs have been shown to be as effective as CBT in the treatment of depressive symptoms in patients with some forms of cancer.[32] In patients with moderate depressive symptoms, psychotherapeutic interventions can be used in conjunction with pharmacotherapeutic approaches, and the outcomes may be better than for either intervention alone.[33]

Pharmacotherapy

In medically ill patients with moderate to severe depressive symptoms, antidepressant pharmacotherapy may be indicated. The decision to use antidepressant medications in medically ill patients needs to include a consideration of side effects, drug–drug interactions and the effect of the medical illness on the antidepressant treatment.

A recent Cochrane review of antidepressants for treating depression in physically ill people included 44 separate studies (3372 patients) conducted over 4–18 weeks.[34] The studies involved patients with a range of medical illnesses, including cardiovascular disease, cancer, renal disease, pulmonary disease, diabetes, HIV/AIDS and neurological disorders (epilepsy, brain injury, multiple sclerosis and IPD). The medications studied included tricyclic antidepressants (TCAs), selective serotonin reuptake inhibitors (SSRIs), serotonin–noradrenaline reuptake inhibitors (SNRIs), mianserin and mirtazapine. Antidepressant treatments were associated with consistently improved efficacy over placebo in nearly all of the studies reviewed, although the effect sizes were moderate (for studies over 6 weeks, the number needed to treat [NNT] was six patients, while in studies of 4–5 weeks or >9 weeks, the NNT was 7). There were very few direct comparisons between antidepressants, but indirect comparisons suggest there were no differences in efficacy between the classes of antidepressants in the treatment of depressive symptoms in medically ill patients. The main adverse events reported in these studies were dry mouth (with SSRIs and TCAs) and sexual dysfunction (with SSRIs). At 6–8 weeks, the number needed to harm was 19. The increased side-effect burden and risk in overdose of TCAs makes them second-line or third-line agents in the treatment of depression in medically ill patients. There is little evidence to support specific antidepressants in the context of individual medical illnesses.

The decision to use antidepressants in medically ill patients requires special consideration of drug–drug interactions and potential alteration of pharmacokinetics secondary to the medical illness. There are two common drug–drug interactions that may involve antidepressants. First, many medications are highly bound to plasma proteins. As most antidepressants also bind strongly to these sites, there is potential for displacement of the initial medication, leading to markedly increased free levels in the plasma and major changes in therapeutic activity. A classic example is the displacement of warfarin by SSRIs, resulting in dangerous elevations of the international normalised ratio. In general, fluvoxamine, escitalopram, venlafaxine and desvenlafaxine have relatively low binding to plasma proteins, making them safer options for patients with medical illness.[35]

The second main type of drug–drug interaction involves the hepatic metabolism of medications via the cytochrome system in the liver. While many medications are metabolised by hepatic cytochromes, resulting in metabolites with either increased or decreased therapeutic activity, the cytochromes themselves can be induced or inhibited as a result of metabolising medications and environmental toxins. The administration of antidepressants

can therefore result in increased levels of other drugs by competitive binding at, or inhibition of, specific cytochromes; or they may cause increased or decreased blood levels. The changes in plasma levels of drugs interacting at the cytochrome level can be as high as fourfold, leading to potentially life-threatening interactions. There is insufficient space here to list the cytochrome binding, inhibition and induction potential of all medications, but caution should be used when prescribing an antidepressant to patients taking other medications. Online drug interaction checking tools are useful resources in this regard (eg, http://www.drugs.com/interactions and http://reference.medscape.com/drug-interactionchecker).

The other consideration when prescribing antidepressants for medically ill patients is the effect of the illness on the metabolism and elimination of the medication. For example, the presence of liver disease may alter the pharmacokinetics of antidepressants by reducing either the production of plasma proteins or the capacity to metabolise the antidepressant, resulting in increased plasma levels of the parent drug, reduced plasma levels of the metabolite, and a prolonged half-life. In general, initial dosing of all antidepressants should be reduced by at least 50% in patients with hepatic insufficiency, and there should be careful monitoring for side effects during the course of treatment and especially after dose adjustment. Desvenlafaxine may be an exception, as it does not undergo oxidative metabolism in the liver; however, caution should be used in patients with severe liver failure. As the metabolites of most antidepressants are eliminated by the kidney, dosage adjustments are frequently required in patients with renal impairment. Most antidepressants require only minor dose reductions in patients with mild renal insufficiency, and around 50% dose reduction in those with moderate renal insufficiency. Individual dose reductions should be informed by the manufacturer's recommendations.

Conclusions

Depressive symptoms are frequently encountered in patients with physical illness. This comorbidity has widespread implications and presents some management problems. Recognition of depression in medically ill patients is the first barrier to treatment, and an emphasis should be placed on psychological symptoms when making the diagnosis. Once recognised, several interventions for depression have been shown to be effective in this patient group, including minimising the disability of the medical illness, general supportive measures, individual CBT, and antidepressant medications in patients with moderate to severe symptoms. When using antidepressant medications, it is important to consider drug–drug and illness–drug interactions when choosing the class of medication and the starting dose.

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