The World Psychiatric Association

WPA Educational Programme on Depressive Disorders

Physical Illness and Depression

volume

two

VOLUME 2

PHYSICAL ILLNESS AND DEPRESSION
Revision of 2008

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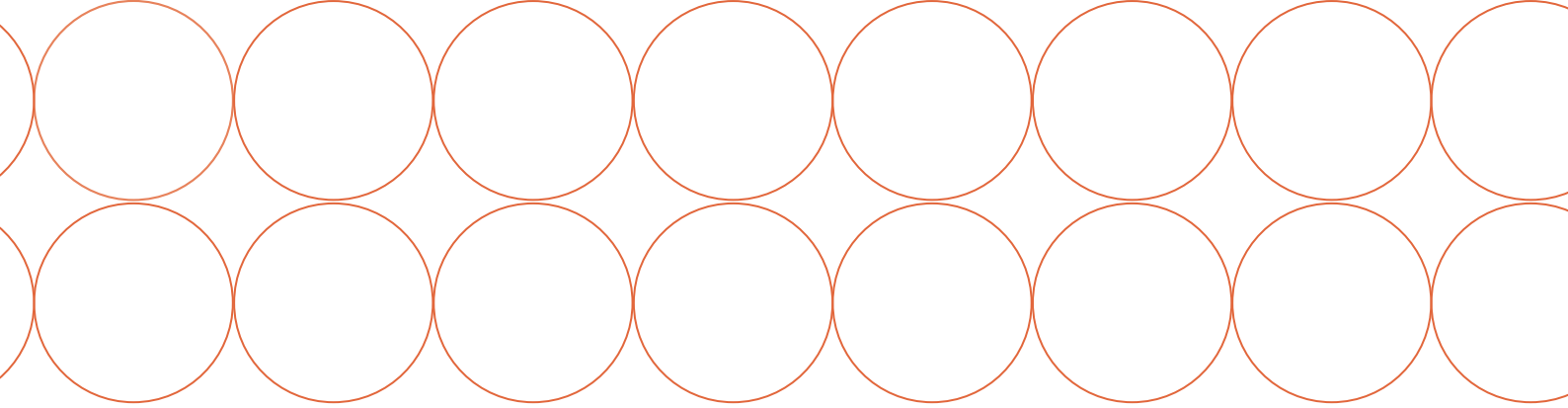
The authors would like to gratefully acknowledge the editing done by Ruth Ross as well as the typesetting and layout design by c|change inc. www.cchangeinc.com



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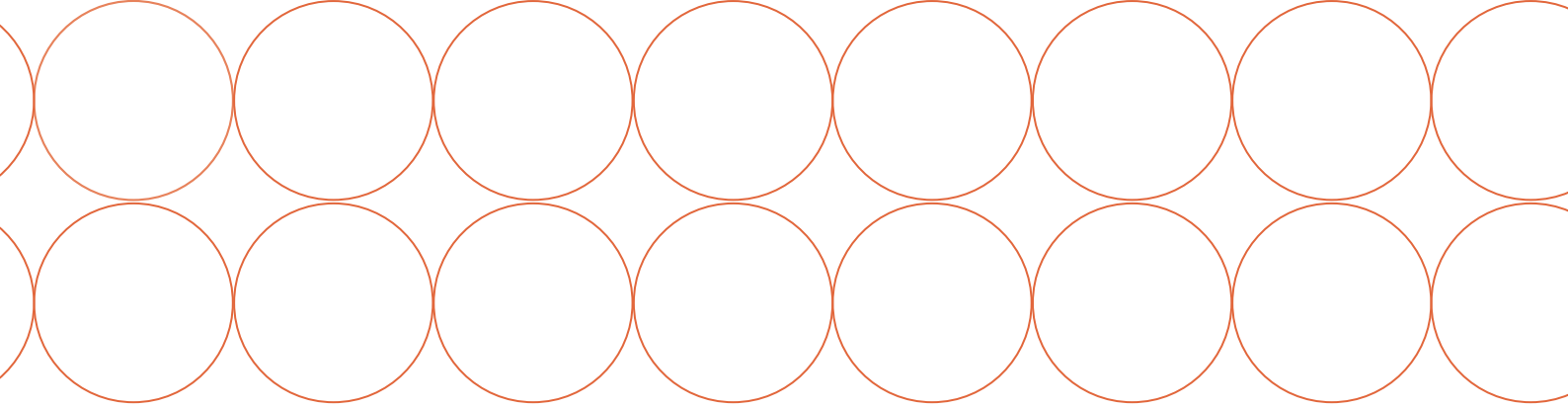

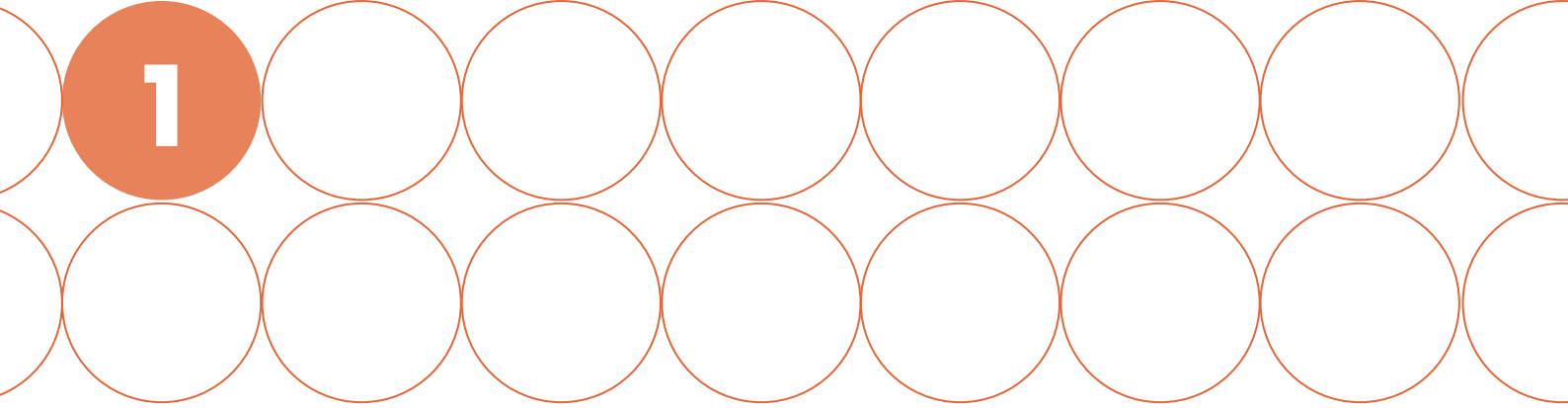

Chapter 1

Prevalence, Pathogenesis, and Diagnosis of Depressive Disorders in the Medically Ill

Rodolfo Fahrer, M.D. PhD. Professor Francis Creed; and Luigi Grassi, M.D.

THE PREVALENCE AND SIGNIFICANCE OF DEPRESSIVE DISORDERS IN THE MEDICALLY ILL

Depressive disorders are among the most frequent conditions seen in primary care. Although figures vary, a large international study recently found median prevalence rates of more than 10% in primary care settings (Üstün and Sartorius 1995). Among patients suffering from a medical illness, the rates are higher—between 22% and 33% for medical inpatients overall, with varying rates for specific illnesses (see Volume I, Chapter 2 "Epidemiology and Impact of Depressive Disorders"). Prevalence rates of depression associated with specific medical illnesses are discussed, where available, in the relevant chapters in this Volume. However, the prevalence rates of depression reported in association with specific illnesses varies widely, due largely to a number of problems that pervade the literature in this area, including disagreement about what constitutes a depressive disorder in the medically ill, lack of validated assessment measures for use in medically ill populations, sociodemographic heterogeneity in the populations examined, and lack of appropriate control groups.

Many studies have examined the relationship between mood disorders and the development, course, and morbidity and mortality associated with selected medical illnesses. A growing body of evidence suggests that biological mechanisms underlie a bi-directional link between mood disorders and many medical illnesses. Thus, depression is frequently comorbid with a variety of medical illnesses, and individuals who have such comorbid conditions may have increased morbidity and lower functional status. Mood disorders can also affect the course of medical illnesses (Evans et al. 2005). Usual antidepressant treatments can be effective in depressed patients with comorbid medical illness; however, these patients have lower rates of recovery and remission of depressive symptoms and higher rates of relapse during follow-up than patients with major depressive disorder (MDD) who do not have comorbid medical conditions. Thus, comorbid medical illness is a marker for treatment-resistance in MDD. In light of these findings, two clinical strategies are recommended: 1) an increased index of suspicion for depression in medically ill patients, and 2) more intensive antidepressant treatment in depressed patients with medical comorbidity (Iosifescu 2007).

Koike et al. (2002) reported that depressed patients with comorbid medical disorders tend to receive treatment at a similar rate but have worse depression outcomes than depressed patients without comorbid medical illness. However, quality improvement programs for depression have the potential to improve treatment rates and outcomes for depressed primary care patients with comorbid medical illness.

Based on a series of qualitative interviews, Clarke et al. (2006) described the experience of hospitalised medically ill patients who were depressed and distinguished experiences that were unique to depression from those that were common to being ill and hospitalized. Theoretical analysis suggests that the experience of depression suffered by hospitalized medically ill patients fits well with the concept of demoralisation described by Jerome Frank (Frank and Frank 1996). Demoralisation, involving feelings of being unable to cope, helplessness, hopelessness, and diminished personal esteem, characterises much of the depression seen in hospitalized medically ill patients.

Over the past 20 years, many exciting discoveries have been made regarding the relationship between depression and the immune system. The findings have increasingly placed the field of psychoneuroimmunology in a clinical context with important translational implications. Depression has been found to have an impact on a variety of immunologically based diseases, including infectious illnesses, autoimmune disorders, cancer, and, based on the most recent findings, cardiovascular disease. Research in this area has established that brain-immune interactions are an essential component in psychiatric and medical comorbidities and have a significant impact on patient health (Irwin and Miller 2007).

Frasure-Smith and colleagues (2007) investigated the impact of depression on inflammatory markers in men 2 months after an acute coronary syndrome (ACS). They found that depression and C-reactive protein, a marker of systemic inflammation, are overlapping prognostic risks, suggesting that patients with either risk may benefit from similar therapies.

Depression is a condition that costs lives and compromises quality of life. Nine out of 10 depressed patients are treated only in primary care, and up to two thirds of suicide victims contact a general practitioner during the 4 weeks before their death. However, depression is often inadequately managed in primary care for a wide variety of reasons (Walters et al. 2005). For example, patients may confuse symptoms, present with somatic symptoms, be unaware of their need for treatment, or go to the doctor too infrequently (Bushnell 2004). General practitioners also sometimes have negative attitudes towards mental health problems and do not feel responsible for addressing them. In addition, they often lack the necessary time, facilities, and knowledge to treat psychiatric problems.

The general risk factors for depressive disorders are the same in people with and without physical illnesses. For example, rates of depressive disorders generally appear to be higher in women, unmarried adults, and those living alone and in those with a history of previous depressive episodes. Addition risk factors can be present in patients with physical illnesses. For example, certain types of medical illnesses as well as treatments for certain illnesses can increase the risk of depression. Not surprisingly, more severe depressive disorders are generally associated with physical illnesses that are more severe, painful, or disabling. However, it is important to note that a significant proportion of patients with physical illnesses do not develop depressive disorders. Thus, it is not true that patients will necessarily be "understandably depressed" by a physical illness. Table 1.1 summarises some key points concerning patients with depressive disorders and physical illness.

TABLE 1.1

Depressive disorders in patients with physical illness

Key Points

- Depressive symptoms are common in the physically ill.
- The likelihood of depressive disorders developing in this population will increase as life expectancy increases.
- Depressive disorders co-occurring with physical illness invariably increase associated psychosocial impairment and often complicate medical rehabilitation and treatment.
- Suicide rates are higher among patients with physical illness than in the general population and are particularly high in patients with certain disorders (e.g., end-stage renal disease, cancer, epilepsy, AIDS).
- Depressive disorders in the physically ill can and must be treated whenever they are diagnosed; postponing treatment worsens the prognosis of both the physical illness and the depressive disorder.

IMPROVING PRIMARY CARE TREATMENT FOR DEPRESSION

Depressive symptoms are common in patients seen in primary care settings, and these symptoms are often severe and may even be life-threatening. Early identification is important in reducing unnecessary suffering, stopping the progression of depression, and preventing it from becoming chronic. Rates of detection for depression can be improved by screening strategies and active investigation (Hegerl and Pfeiffer-Gerschel 2007).

Practitioners who treat the medically ill—generalists and specialists alike—are likely to have patients who are suffering from comorbid depressive symptoms and disorders, which, in turn, may significantly exacerbate their physical illnesses. Understanding the clinical characteristics that differentiate symptoms of depressive disorders from symptoms of physical illness can facilitate clinical management in this situation. The primary care physician is the first medical contact for the vast majority of patients with depression. The key to successful primary preventive strategies lies in improved detection of patient groups at risk.

We recommend the following strategies as a means of improving detection, treatment, and prevention of depression in primary care and other general medical settings:

1. Improve and encourage teaching of psychiatry to primary care physicians and other medical specialists, as well as to medical students and other health workers.

2. Promote methods of observation and training in psychological skills and techniques that will enable physicians to gain a more holistic understanding of patients with physical illness.

3. Provide improved opportunities for primary care and other medical practitioners to acquire a basic background in psychiatry and a better understanding of psychophysiological, eco-epidemiological, psychopathologic, and therapeutic techniques.

4. Encourage a more integrative, multidisciplinary teamwork approach to research, training, and patient care.

5. Develop preventive and therapeutic resources within communities to address individual, family, and/or group crises.

6. Promote research and teaching concerning diagnostic and therapeutic methods that can be used in family disturbances and place more emphasis on the role of the family in promoting mental health in the community.

7. Provide solutions to help clinicians overcome problems in doctor-patient relationships caused by insurance and prepaid healthcare systems.

A variety of strategies are available to improve community mental health and prevent mental disorders, including depression. Such interventions may target a) factors that contribute to the development of or help maintain illnesses; b) specific population groups (e.g. the population over 60 years of age, which will have exceeded 1.2 billion worldwide by the year 2025); and c) particular settings (e.g. schools to help them teach life skills that foster healthy social and emotional development). It is also important to provide and regularly assess continuing medical education that focuses on improving the detection and treatment of depression in physically ill patients.

Although training opportunities vary, specific psychiatric training generally takes place in three main settings: during work in a psychiatric setting as part of a vocational training program; during a trainee appointment; and in continuing medical education. General practitioners should be trained to understand and manage depression, fight stigma; and integrate psychosocial and psychiatric elements in their daily medical practice. Other specialities need to acquire a greater recognition of the value of psychiatry. Initiatives are needed that emphasise the importance of mental health to the community and the need for a global effort to provide better training in the behavioural sciences and psychotherapy to all physicians. Teaching of psychiatry in medical schools should combine both

theory and practice, and programs should include clinically relevant subjects such as diagnosis of psychiatric disorders, psychopharmacology, psychotherapy, interview skills, and therapeutic doctor-patient relationships. Effective approaches to teaching and learning of psychiatry may include self-directed learning based on problem-solving; locally developed teaching tools; practice with a wide range of patients in different settings; and integration of psychiatric teaching and learning in medical school curricula. Primary care physicians need to be acquainted with the main types of antidepressant medications and their indications, contraindications, side effects, and potential interactions; the major psychotherapy techniques used to treat depression; and principles of social treatment and rehabilitation. The well trained primary care physician will have the skills needed for early detection and treatment of depression in physically ill patients (Fahrer 2002). To properly prepare the general practitioner, the psychiatrists involved in such training need to have a) a medical identity, b) training in psychiatry with a sound basis in psychotherapy, and c) teaching skills that allow them to work effectively in a non-specialised medical settings. Seminars to train psychiatrists to provide this kind of teaching should stress uniform clinical and therapeutic criteria for depression and techniques for interviewing colleagues and leading workshops and seminars (Fahrer 1999).

PATHOGENESIS

As with many other diseases, a host of neurobiological, developmental, and psychosocial factors can influence the development and course of depressive disorders (Soutwick et al. 2005). Genetic and familial factors play a role, as do personality traits and negative life events (e.g., loss of a job, change in social status). For a more general discussion of factors that can influence the development of depressive disorders, see Volume I, Chapter 4 "Aetiology and Pathogenesis of Depressive Disorders". Studies have shown that certain medical conditions are associated with depressive disorders. When a person suffers from a concomitant medical condition, such as a neurological, cardiovascular, oncological, or endocrine disorder, causality is often difficult to determine. When a depressive disorder and a medical condition co-occur, four possible situations may be involved:

1. The medical condition may predispose the patient to develop a depressive disorder.
2. The depressive disorder may predispose the patient to develop a medical condition (Table 1.2).
3. The medical condition and the depressive disorder may share genetic and/or environmental factors that predispose the patient to both types of disorders.
4. The two disorders may have developed independently of each other.

TABLE 1.2

Depressive disorders as a cause of physical illness

Depressive illnesses can precede and possibly cause or contribute to physical illnesses in the following ways:

- Immunological mechanisms: decreased natural killer cell activity or other physiological changes (eg., hypercortisolemia) could act as an immunosuppressant and lead to compromised immunity.
- Self-neglect may lead to new or worsening physical illness.
- Treatment for the depressive disorder itself can cause medical problems (e.g., heptic or cardiac dysfunction) (Volume I, Chapter 3 for a more detailed discussion of depression treatment).
- Suicide attempts, even when unsuccessful, may have physical consequences.

Physical Illness as a Cause of Depressive Disorders

Physical illness may cause depressive disorders via physical/biological or psychosocial mechanisms.

Biological mechanisms

Various factors, which are supported by recent research, have been proposed as possible biological mechanisms by which a physical illness might induce a depressive disorder. Although we describe these factors separately in the sections that follow, it is important to keep in mind that these different mechanisms are likely to interact and influence one another.

Impairment of neurochemical pathways and structures that modulate mood states

Studies suggest that parallel functional interruption of the neural networks that connect the basal ganglia and the prefrontal cortex may functionally or structurally affect mood, cognitive processes, and motor function (Alexander et al. 1986; Parker and Hadzi-Pavlovic 1996). This process may be involved in neurological diseases, such as Parkinson's, Huntington's, or multiple sclerosis, as well as in stroke, where vascular factors may also play a significant role in causing depression (Camus et al. 2004) (see Volume II, Chapter 2 "Depressive Disorders in Patients with Neurological Disorders"). Brain tumours and other lesions may also directly disrupt these neural pathways. The majority of studies have also indicated that chronic activation of the Hypothalamic-Pituitary-Adrenal (HPA) axis and cortisol, found in association with major depression (see below), causes a glucocorticoid-dependent reduction in volume, dendritic arborization, and neurogenesis in the hippocampus, an important brain area that plays a role in learning and memory processes in depressed patients (Colla et al. 2007; Dranovsky and Hen 2006). Proinflammatory cytokines secondary to physical illness (see below) can also affect neurochemical pathways in the brain.

Endogenous cytokines and compromised immune function

Depressive symptoms are common following infection, perhaps because of cytokine release or other immunological perturbations. Pro-inflammatory cytokines such as interleukin-1 (IL-1) and interleukin-6 (IL-6) are potent modulators of corticotropin-releasing hormone (CRH). Such activity may in turn modulate the activation of the HPA axis by CRH via a secondary increase in adrenocorticotropin hormone (ACTH) and cortisol, elevated levels of both of which have been reported in individuals with major depression (Raison et al. 2006; Schiepers et al. 2005). Physical diseases themselves, as well as the treatments for those illnesses (e.g., drugs, surgery), together with the individual stress response, can result in the production of pro-inflammatory endogen cytokines, which may contribute to the development of depressive symptoms (Kronfol and Remick 2000).

Effects on neurotransmitters

It has been suggested that the disruption of neurotransmitters may explain the higher incidence of depression in certain physical illnesses. For example, in pancreatic cancer, increased urinary 5-HIAA could be a marker of reduced serotonin availability at the synapses. It is possible that proteins released by cancer cells induce antibodies, which bind to serotonin receptors, or that anti-idiotypic antibodies act as alternative receptors for serotonin It is also possible that cytokines play a role in this situation, since pro-inflammatory cytokines are involved in activating the enzyme indoleamine-2,3-dioxygenase (IDO). Active IDO catalyses the rate-limiting step of tryptophan conversion into kynurenine and then quinolinic acid, reducing the availability of tryptophan for conversion into 5-HT (Irwin and Miller, 2007). Both kynurenine and quinoloic acid are neurotoxic substances that can promote the excretion of cortisol by acting on the HPA axis.

Genetic factors

Recent research has demonstrated a relationship between genes and susceptibility to major depression. Studies have shown that a polymorphic region (5-HTTLPR) in the promoter region of the gene for the uptake of 5-HT may predispose a person to depression. In particular, the short "S" allele variant of the 5-HT promoter is associated with a higher risk of depression, while the long "L" allele variant is associated with more resistance to the development of depression. The risk of developing depression is enhanced by stressful events, including the development of a physical illness. The effect of stressful life events on

depressive symptoms in young adults was found to be significantly stronger among SS or SL subjects than among LL subjects (Caspi et al. 2003; Kim et al. 2007). In addition, Wurtman (2005) reported that mutations in the gene that controls serotonin synthesis in the human brain (tryptophan hydroxylase) also predispose individuals to mood disturbances.

Disturbances in endocrine function

An imbalance of the HPA axis with a secondary increase in levels of ACTH and cortisol, similar to that observed in Cushing's syndrome, is often observed in individuals experiencing chronic psychosocial stress; this phenomenon may be related to major depression. As described above, disturbances in endocrine function can have negative effects on brain structure (e.g. hippocampus) and immune function. Depressive symptoms can occur following some endocrine disease, such as hypothyroidism and Cushing's syndrome (See Volume II, Chapter 5, "Depressive Disorders in Patients with Endocrinological Disorders").

Psychosocial Mechanisms

Impact of illness on the patient

Physical illness is often accompanied by pain, suffering, and a loss of status, as well as a loss of health. The patient is faced with a reduced ability to function and carry out activities of daily living. If the person is hospitalized, he or she must also cope with a new and potentially frightening environment. Patients with physical illnesses may also be experiencing severe financial stress, the threat of job loss, a major disability, or a threat to their lives.

Cassell (1979) describes responses to physical illness in psychodynamic terms as a loss of the sense of "indestructibility" that serves as a shield essential to normal functioning, leaving the individual feeling fragile and defenceless; a feeling of being disconnected from the world both socially and existentially; a failure of logic characterised by "magical thinking" (e.g., conviction that the disease doesn't really exist or will go away); and a loss of a sense of control over one's life, resulting in feelings of helplessness.

When physical illness is experienced as a loss—of health, control, or current or future possibilities—the patient may experience a grief state similar to that which occurs after the loss of a loved one. The person may thus go through the component grieving phases of denial, protest and anger, bargaining, and eventual acceptance. However, feeling significantly depressed is not always a feature of the grieving process that may occur in physical illness. As in uncomplicated grief, patients may describe a sense of loss but not suffer from a depressive disorder; they may loathe being ill and loathe the illness—but not loathe themselves. Given the interconnectedness of illness and depressed feelings, why is it that only a subset of those with physically illness develop a depressive disorder? In addition to variations in genetic predisposition, some patients may "mourn" the losses appropriately and adapt to the illness. In contrast, when the illness and its consequences are severe, or the patient's sense of self is fragile or closely tied to physical status or bodily appearance, the person may be at particular risk for developing a depressive disorder, especially if the illness involves marked disability or disfigurement or undermines the patient's sense of mastery. Since bodily experience is the precursor of a psychological sense of self and contributes to one's self-experience throughout life, the degree to which an individual has a sense of relatedness to his or her body could be a key determinant of the severity of the person's emotional response to illness (Rodin et al. 1991).

Social support

Since physical illness increases an individual's need for support, lack of social support can contribute to a depressive disorder. Adequate social support may reduce the likelihood of an individual's developing a depressive disorder by partly attenuating the effects of stress. However, individuals vary greatly in their need for social support, and such needs are very much influenced by personality factors. An interplay among stressful events, personality traits (e.g., external locus of control), and poor social support has been shown in medically ill patients, such as those with HIV (Grassi et al. 1999) and cancer (Grassi et al. 1997). The patient's perception of social support from those close to him or her and from medical and nursing staff may

also be important, regardless of the extent to which such support is actually provided. Regardless of why a depressive disorder develops in the setting of medical illness, it is important to remember that, in the vast majority of cases, the depressive disorder can be successfully treated. There is no reason for individuals who are already medically ill to endure the additional pain and suffering associated with a depressive syndrome.

Interactions Between Depressive Disorders and Physical Illness

A co-existing depressive disorder and physical illness may interact in ways that increase the effects of one on the other. For example, Kartha et al. (2007) reported that depressed patients in medical wards had worse outcomes than non-depressed patients at several follow-up intervals. Another study demonstrated that physically ill patients with depressive disorders are more likely to have higher rates of rehospitalisation, an increased risk of complications from their medical disease (e.g. heart disease, cancer) (see Volume II, "Chapter 3. Depressive Disorders in Patients with Cardiovascular Disease" and Chapter 6 "Depressive Disorders and Oncology") and a poorer prognosis (von Ammon Cavanaugh1995).

Personality factors may predispose a patient to both a depressive disorder and a poorer outcome of his or her physical illness—either directly, as when the patient refuses to adhere to treatment, or indirectly, via a compromised capacity to be involved in rehabilitation. For example, an inability to express their feelings (alexithymia) has been associated with depression among hemodialysis patients, independent of the degree of social support they receive (Kojima et al. 2007).

Fortunately, it has been shown that active treatment of a depressive disorder can improve outcomes in several physical illnesses, in terms of quality of life, return to work, and possibly biological resilience. Effective treatment of depression has also been shown to restore the disturbed interplay between cytokines and the HPA axis (Himmerich et al. 2006) and reverse neuronal alterations in the hippocampus caused by chronic stress and depression (Krystal 2007).

Pharmacogenic Factors

A significant amount of data are available concerning prescribed medications that may contribute to depressive symptoms (Kotlyar et al. 2005; Patten and Barbui 2004) The concept of cytokine-induced depression (or sickness behaviour) has been introduced to describe a depression-like disorder directly determined by certain exogenous cytokines that are used to treat medical disorders. Interferon-alpha, a drug which is used to treat Hepatitis C, melanoma, and multiple sclerosis, is an example of an agent that is clearly associated with the onset of depression in predisposed individuals (Capuron and Miller 2004). Capuron and Miller (2004) have suggested that exogenous cytokines determine mood and cognitive symptoms of sickness behaviour via a hyper-responsiveness of the CRF pathway and altered 5-HT metabolism. They also suggested that vegetative symptoms are more related to possible alterations in basal ganglia activity caused by cytokines. A comparison of the symptoms that characterise cytokine-induced depression (sickness behaviour) and major depressive disorder is presented in Table 1.3. Note that worthlessness, guilty feelings, and suicide ideation are characteristic features of major depression but not of cytokine-induced depression. It has also been suggested that depression may occur in association with calcium-channel blockers, chemotherapeutic agents, and certain antibiotics. Benzodiazepines, including hypnotics and antipsychotic medications, especially conventional agents such as haloperidol or chlorpromazine, may be useful as adjuncts to antidepressants for the treatment of anxiety symptoms. However, benzodiazepines may interact with antidepressants or may trigger depressive symptoms upon withdrawal.

Table 1.4 presents a list of drugs that may be associated with depressive symptoms. More detailed discussions of medications used to treat specific medical disorders, their potential to cause depression, and possible interactions between those medications and antidepressants are provided in the disorder-specific chapters of Volume II. A discussion of depression and substance abuse disorders is provided in Volume II, Chapter 10.

TABLE 1.3

Comparison of the symptoms of

Major depressive disorder	Cytokine induced depression (sickness behaviour)
• Depressed mood	• Depressed mood
• Anhedonia	• Anhedonia
• Hoplessness-helplessness	• Helplessness
• Worthlessness	
• Guilty feelings	
• Suicide ideation	
• Fatigue	• Fatigue
• Anorexia/weight loss	• Anorexia/weight loss
• Hypo/hypersomnia	• Hypersomnia
• Psychomotor retardation/accelaration	• Psychomotor retardation
• Decreased concentration	• Decreased concentration
• Cognitive impairment	• Cognitive impairment

TABLE 1.4

Medications that may be associated with depressive symptoms*

Antiarrhythmic Drugs • Digitalis • Procainamide	Antibiotics • Amphotericin B • Cycloserine • Dapsone • Ethionamide	Anticholesterol Drugs • Cholestyramine • Statins	Anticonvulsants • Felbamate • Phenobarbitone • Vigabatrin
Antihypertensive Agents • Beta blockers (lipophilic) • Clonidine • Methyldopa • Calcium channel blockers • ACE inhibitors	Antinflammatories • NSAIDs • Interferon	Cancer Chemotherapy Agents • Asparaginase • Methotrexate • Procarbazine • Vinblastine	H2 Blockers • Cimetidine
Hormonal Agents (Withdrawal) • Anabolic steroids • Corticosteroids • Oral contraceptives	Lipid-Lowering Drugs • Simvastatin	Psychotropic Drugs • Benzodiazepines • Neuroleptics • Methaqualone • Stimulants	Selective Estrogen Receptor Modulators • Tamoxifen

*Depressive symptoms are not the same as depressive disorders.

IDENTIFICATION, DIAGNOSIS, AND MANAGEMENT

The clinical interview is the cornerstone in diagnosing a suspected depressive disorder in a physically ill patient. After putting the patient at ease and asking a few open-ended questions (e.g., "How are you feeling today?"), it is useful for the interviewer to take a complete medical history before proceeding to more specific queries and administration of a well-recognised screening questionnaire. (See Volume I, Chapter 3 for a general discussion of clinical interview and assessment strategies for depression.)

The presence of the following clinical characteristics can help clinicians diagnose depressive disorders in medically ill patients:

- Typical psychological and somatic symptoms of depressive disorder
- Family history of depressive disorders/mania/hypomania
- Family history of suicide/suicide attempt
- Previous depressive episodes/good response to antidepressants in the past
- Previous manic or hypomanic episodes
- Previous suicide attempt(s)
- History of alcoholism or alcohol abuse and/or substance abuse disorders
- Seasonal variation and/or diurnal variation of depressive symptoms that do not parallel those of the medical illness
- Self-blaming, guilt, psychotic symptoms (delusions), suicidal ideation

Screening tools may be used in addition to, or before, the clinical interview. Table 1.5 lists examples of tools specifically designed to detect depressive disorders (note that not all of these screens have been translated from English into other languages or adapted for use in other cultural settings). A screen should never be used as the sole determinant of a diagnosis, and the "cut-off" score that is said to denote probable depressive disorder may need to be raised in the physically ill as some symptoms may be associated with specific medical illnesses as well as depressive disorders (Creed and Dickens 2007).

Obstacles to Diagnosis

An open doctor-patient relationship can play a crucial role in the rapid detection and effective management of depressive disorders. While interviewing the patient and taking his or her history, it is important that clinicians be aware of the following potential confounders:

- **Medical symptomatology:** As noted above, the presence of a serious comorbid medical illness can obscure a depressive disorder, since many symptoms (e.g., fatigue, loss of appetite) may be common to both.
- **Denial:** Physically ill patients may be reluctant to report depressed mood, perhaps because they fear it may compromise their medical treatment. Conversely, denial mechanisms invoked to deal with the physical illness may lead patients to disavow or suppress psychological symptoms. Denial is particularly likely when family members and/or other caregivers implicitly demand a an optimistic atmosphere that downplays symptoms. When patients seek to discuss a depressed mood, they should not be interrupted or family members and medical staff should not invalidate or minimise their symptoms.
- **Somatisation:** Some patients may deny a depressed mood but describe their disorder in somatic terms. Especially in general medical settings, this may lead to investigations for other physical illnesses because both doctors and patients are "focused" on physical causes of symptoms. The greater number of different bodily symptoms a patient mentions, the more likely that a comorbid depressive illness may be present.
- **Tacit collusion** may occur when discussion of depressive symptoms is perceived as being uncomfortable, stigmatising, or too time consuming. Even when depressive symptoms are recognised, they may be minimised while attention is focused instead on the medical illness.

TABLE 1.5

Tools helpful in identifying, diagnosing, and evaluating the severity of secondary depressive disorders

Scale	Description	Type
Beck Depression Inventory (BDI) (Beck 1961)	Identifies depressed patients through a self-administered questionnaire	Self-report
Center for Epidemiological Studies–Depression Scale (CES-D) (Radloff 1977)	Used for depression research in the general population	Self-report
Geriatric Depression Scale (GDS) (Yesavage and Brink 1983)	Especially helpful in screening older patients	Self-report
Hospital Anxiety and Depression Scale (HADS) (Zigmond and Snaith 1983)	Designed specifically for use in medically ill patients because it excludes bodily symptoms	Self-report
Hamilton Depression Scale (HAM-D) (Hamilton 1967; Paykel 1990)	Rating scale containing symptoms of depression	Clinician rated
Montgomery Asberg scale (MADRS) (Montgomery and Asberg 1979)	Rating scale containing symptoms of depression	Clinician rated
Standardized Assessment of Depressive Disorders (SADD) (Sartorius and Davidian 1983)	Instrument for recording results of clinical assessments of patients with depressive disorders	Clinician rated
Zung Scale (Zung 1965)	A questionnaire useful for primary care practice	Self-report

Note: When screening and diagnostic tools are used, a depressive disorder should not be diagnosed on the basis of somatic items alone (e.g., anorexia, fatigue). Such features c an be included as diagnostic symptoms, but some researchers recommend that somatic symptoms be given less weight than mood state items, such as suicidal ideation, guilt, a sense of failure or feeling like a burden, and frequent crying (Endicott 1984). In additional, because no categorical cutoff scores can reliably distinguish a "case" from a "noncase" in this population, case threshold and severity cutoff scores should be increased in evaluating patients with physically illness to avoid overrating or overdiagnosing depressive disorders (Cavanaugh, 1995).

To determine whether depressive symptoms may be related to medications being used to treat the patient's physical illness, it is useful to explore the patient's medication history. This involves determining whether the individual has had previous episodes of medication-induced depressive disorder, is taking any new medications, or if the dosage of a medication that the person takes regularly has recently been changed. It is also important to ask about medications that the patient may consider "unimportant," such as contraceptive pills and eye drops, as well as medications that have side effects that may mimic depressive symptoms, such as sedative-hypnotic drugs. The doctor should also ask about herbal medicines and homeopathic agents; although most patients do not volunteer information about such alternative agents, they can have important effects in terms of drug interactions.

To assess whether physical illness is a contributing cause of depressive symptoms, the history should determine the time course of both the depressive symptoms and the symptoms that are clearly attributable to the physical illness; a thorough medical assessment should also be done. Laboratory evaluation, including blood levels of drugs when appropriate and available, may also be useful.

It is important to remember that depressive disorders, once recognised, are highly treatable, and that appropriate treatment for depression will often reduce the disability associated with comorbid medical illnesses and may also help improve bodily symptoms, especially pain.

Treatment Options

Depressive disorders usually can be managed successfully within the framework of the primary care physician's practice. However, certain patients will require consultation with or referral to a specialist. Spending adequate time in making the diagnosis and providing in patient and family education during the early phase of treatment will save time in the long run and provide comfort and reassurance to everyone concerned. It is essential that the patient and his or her caregivers understand the reason for antidepressant treatment in order to reduce adherence problems (Ziegelstein et al 2000).

After a depressive disorder is diagnosed, the principal aim of treatment is to decrease symptoms, reduce disability and suffering, and have a favourable effect on the course of the medical illness. Depressive disorders are closely associated with impaired health-related quality of life. As a result, successful treatment of depression can have an important impact on quality of life (Creed et al. 2002; 2003). Treatments with the highest probability of success and lowest risk of adverse events should be tried first whenever possible.

Any depressive disorder is likely to benefit from antidepressant medication, although the patient's willingness to take additional medication should be assessed prior to prescribing such drugs. Techniques to improve adherence—for example, support and encouragement from a nurse—as well as problem-solving and case management can promote good results in the treatment of depression in patients with physical illness (Katon et al 2004; Lin et al 2003). Cognitive-behavioural therapy techniques may also be helpful in counteracting marked negative perceptions of the physical illness and its effect on the patient, which are frequently exacerbated by the depressive disorder.

It is important that clinicians be aware of the potential for interactions between antidepressant medications and drugs that are commonly used to treat medical illnesses (Table 1.6). If a particular medication or drug interaction is thought to be causing depressive symptoms, the symptoms may resolve simply if the medication is discontinued. The decision to discontinue a medication should be made on an individual basis, weighing the benefits against the potential risks (e.g., toxicity) of continuing the drug. Such decisions require an awareness of the potential efficacy and complications of alternative treatment options and a close interaction between the primary care physician and the psychiatrist.

If the depressive disorder resolves after a drug is discontinued, the clinician can try a different medication to treat the medical illness if one is available. If a change of medication is not practical because an effective alternative is not available (i.e., the alternatives for treating the physical illness are clearly inferior to the original drug), it may be appropriate to restart the original drug in

TABLE 1.6

Potential interactions between antidepressant medications and agents commonly used to treat medical illness

For more detailed discussion of potential drug interactions see Coffman 2002; Cohen 2004; Crone 2006; de Vane 2000; Harpole 2005; Kapur and Kambhampati 1992; Katona 2001; Maxmen 1991; Robinson & Levenson 2000; Robinson & Qaqish 2002; Thompson et al. 2006; Wynn et al. 2007

Potential Interactions between...	Mechanizm	Clinical Effects
Heterocyclic antidepressants and		
Monoamine oxidase inhibitors (MAOIs)	Increased synaptic availability of neurotransmitters	Hypertensive reactions
Cimetidine	Inhibition of metabolism	Increased heterocyclic levels, increased adverse effects
Antipsychotics	Additive anticholinergic and antiadrenergic effects, mutual inhibition of metabolism	Increased anticholinergic and orthostatic side effects
Stimulants	Inhibition of heterocyclic metabolism	Increased heterocyclic blood levels, increased side effects
Phenytoin	Reduced blood level	Increased risk of seizures
Pressor agents	Increased central adrenergic transmission	Clinician rated
Selective serotonin reuptake inhibitors (SSRIs) and (via interference with the cytochrome P450 enzyme system)		
Heterocyclic antidepressants	Inhibition of metabolism	Increased heterocyclic blood levels, increased toxicity
MAOIs	Synergistic serotonergic enhancement	Hypertensive hyperthermic reaction
Theophylline	Inhibition of microsomal liver enzymes	Increased side effects
Antipsychotic drugs	Antidopamine effect of SSRIs, inhibition of microsomal liver enzymes	Increased side effects
Beta-blocking agents	Possible serotonergic effect	Increased risk of cardiac conduction defects
MAOIs and		
Heterocyclic antidepressants	Synergistic "neurotransmitter"	Hypertensive reaction enhancement
Tyramine-rich foods	Increased synaptic tyramine	Hypertensive reaction
Pressor agents, stimulants, sympathomimetics	Increased synaptic availability of catecholamines	Hypertensive reaction
Narcotics	Possibly increased serotonergic transmission	Hypertensive-hyperthermic reaction

combination with an antidepressant medication. For example, while interferon is often necessary for the treatment of hepatitis, it also frequently leads to depression, which may reach a level that fulfils DSM diagnostic criteria for major depressive disorder in approximately a third of patients (Bonaccorso et al, 2002). Psychiatrists may then be asked to consult about the treatment of these patients. Antidepressants have been found to be effective in treating interferon-induced depression, with selective serotonin reuptake inhibitors (SSRIs) used most successfully (Creed and Olden 2005). If the antidepressant medication must be discontinued, doses should be tapered over at least 1 month, since abrupt discontinuation may result in a depressive relapse (for more discussion of the treatment of depression in patients with hepatitis, see Volume II, Chapter 7).

The role of the cytochrome P450 system

It is important that clinicians become familiar with the increasingly recognised interactions involving induction or inhibition of hepatic drug-metabolising enzymes, such as the cytochrome P450 system (Nemeroff et al, 1996). The cytochrome P450 enzyme family plays a major role in oxidative drug metabolism. SSRIs and other drugs may inhibit members of the cytochrome P450 enzyme system to varying degrees. In addition, 5%–6% of Caucasians lack the CYP2D6 isoenzyme (and are thus called poor metabolisers). Thus, some drug-drug interactions may be due to effects on hepatic metabolism (Table 1.7).

Nondrug Therapy

The following therapies may be helpful when use of drugs is particularly hazardous to the patient:

- Cognitive-behavioural or interpersonal therapy is recommended primarily for patients with mild to moderate non-psychotic nonsuicidal depressive disorders (Scott 1996). These treatment modalities can be used either alone or in combination with psychotropic medication.
- Light (photo) therapy is recommended when depressive disorders show fall-winter seasonality (seasonal affective disorder) and may also be used in combination with antidepressants. Standard protocols are available for use of phototherapy (Rosenthal et al. 1984; Terman et al. 1989; Wetteberg, 1994).
- ECT may be successful in cases where the general medical and cardiovascular condition of the patient does not contra-indicate use of brief narcosis and muscle relaxation (Sartorius 1993).

Social Support

Social support may have an impact on outcome in major physical illness (Barry et al. 2006; Dickens et al. 2004; Weihs et al. 2005). It can also moderate the relationship between depression and physical illness (Mohr and Genain 2004). Social support should not be considered as a constant variable; rather, the type and extent of support a patient needs fluctuates across different stages of illness. In the early stages, patients may need reassurance that all is well; later, they may require more specific educational and supportive techniques. Physicians who want to provide optimal help for a patient should assess the social support available to the patient and endeavour to engage relatives or caregivers who can help the patient. For example, because of its importance in good outcomes, heart disease treatment programs have been designed specifically to improve social support in order to reduce depressive symptoms (Berkman et al. 2003).

TABLE 1.7

The cytochrome P450 enzyme system and drug metabolism[a]

CYP1A2	CYP2D6		CYP3A4
amitriptyline caffeine	Antiarrhythmics	Opiates	Antiarrhythmics
clomipramine imipramine Paracetamol (acetaminophen) phenacetin propranolol theophylline	encainide flecainide exiletine ropafenone	codeine dextromethorphan thylmorphine	lidocaine propafenone quinidine
	Beta Blockers	SSRIs	Benzodiazepines
	alprenolol bufurorol metoprolol propranolol timolol	fluoxetine N-desmethyl-citalopram norfluoxetine paroxetine	alprazolam bromazepam midazolam triazolam
	Miscellaneous	TCAs	Calcium Channel Blockers
	amiflamine indoramin perhexiline phenformin tomoxetine warfarin	amitriptyline clomipramine desipramine trimipramine	diltiazem felodipine nifedipine verapamil
	Antipsychotics		Miscellaneous
	haloperidol thioridazine zuclopenthixol		carbamazepine cortisol (hydrocortisone) cyclosporine erythromycin ethinyl estradiol
fluvoxamine*	fluoxetine* paroxetine* ? sertraline*		fluoxetine* fluvoxamine* ? citalopram* ? paroxetine*

[a]Adapted from Askinazi 1996; Lane et al, 1995; Shapiro et al, 1997

*Clinically relevant enzyme inhibition that does not necessarily occur in all cases. Occurrence depends on the dose of the drug, coadministered drugs, the activity of the enzyme, and the general condition of the patient.

Being a "Good Doctor"

Although medical science provides information about biological and related processes, the art of being a "good doctor" includes assessing what the illness means emotionally to the patient (e.g., actual and symbolic losses) and the extent of the patient's coping abilities. To help the patient come to terms with the medical illness as well as concomitant depressive symptoms, the physician should first ask the patient how he or she feels about the illness and then discuss the significance of the illness with a view to reducing demoralisation, encouraging mastery, and addressing specific depressogenic factors. In many cultures, humanitarian interaction with the doctor is valued as much as, if not more than, the doctor's technical or scientific knowledge. The value of such interactions will be enhanced if the doctor deals with the patient in a way that is appropriate to the patient's family background and shows respect and acceptance for local cultural and spiritual norms.

The primary care physician, particularly one who knows the patient and family, is in an excellent position to form a therapeutic alliance with the depressed patient and help him or her overcome potential obstacles to adherence to recommended medical treatment, including pessimism, poor motivation, low energy, guilt, and social isolation. Even mild depressive symptoms can be helped by antidepressant medications and by combining pharmacological, psychological, and social interventions.

Liaison with a psychiatric service is available to primary care physicians in an increasing number of countries and settings. It may appropriate to seek such psychiatric consultation, when available, for a variety of reasons, including diagnostic clarification, advice on management, and possible transfer of care. A responsive liaison service can be very helpful to referring doctors, and a prompt response should be the norm once a psychiatric referral is made. The liaison psychiatrist should undertake a comprehensive assessment that includes taking a complete psychiatric history and performing a mental state examination. Effective communication between the liaison psychiatrist and the referring doctor and other relevant agencies is crucial, and the liaison psychiatrist or his or her nurse should provide follow-up when appropriate and necessary. A fully developed consultation service can also provide multidisciplinary education and staff support and an active educational programme for specialist physicians and primary care doctors.

When Is Referral Appropriate?

Referral to a psychiatrist may be appropriate when the physician:

- Discovers the patient is seriously depressed and suffers from a severe major depressive disorder, long-standing dysthymic disorder, melancholia, or psychotic depression and/or presents with suicidal ideas
- Needs advice regarding the use of psychotropic medications (for example, use of antidepressants in a patient with chronic pain)
- Determines that the depressive disorder is resistant to standard antidepressant treatment
- Finds serious impairment of social functioning that cannot be explained by the presenting illness
- Learns that the patient has a history of sexual abuse or other major trauma that requires more specialised psychological treatment than the physician or general practitioner can provide
- Learns that the patient is being treated for another psychiatric disorder, such as schizophrenia
- Is treating a patient who has not responded to treatment after 4-6 weeks and for whom a change of antidepressant medication, polypharmacy, or ECT may be needed.

Referral may also be appropriate when a patient develops a depressive disorder while taking multiple medications, several of which could be interacting and/or contributing to the depressive symptoms.

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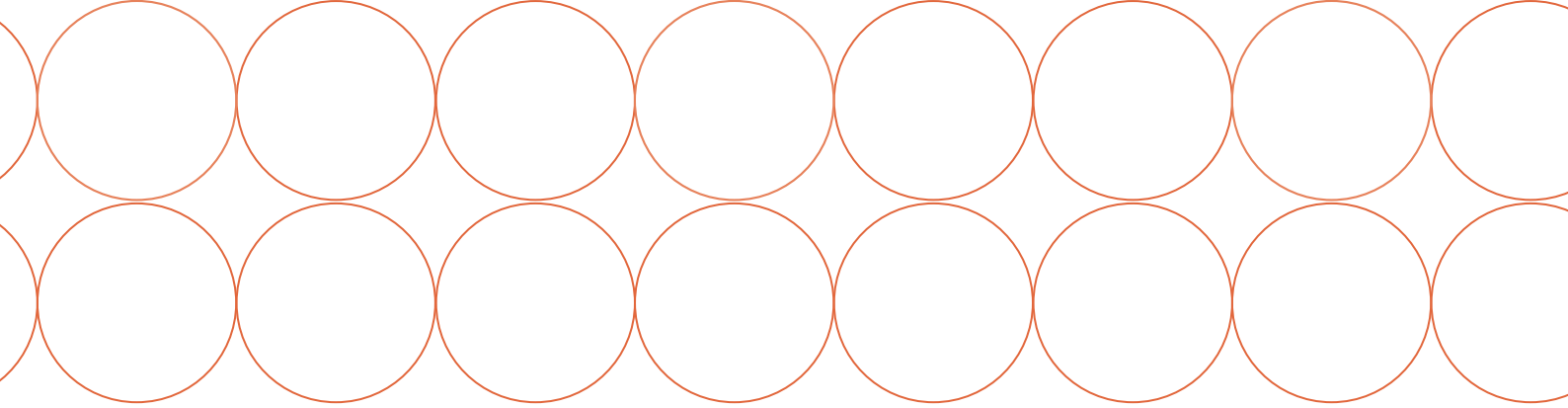

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Chapter 2

Depressive Disorders in Patients with Neurological Diseases

Depressive symptomatology is common in individuals with neurological illnesses, although the relationship between symptoms and specific disorders is complex. A recent book edited by Lyketsos et al. (2006) examined this subject in detail and documented much of the information presented in this chapter.

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EPILEPSY

A relationship between depressive disorders and epilepsy has been described since antiquity, and historical figures such as Hippocrates and Aretaeus discussed the close relationship between the two (Lewis 1934). Epilepsy affects approximately 0.4%–1.0% of the population in the developed world. Kanner (2003b) reported that 6%–30% of all patients with epilepsy, and as many as 50% of those seen in clinical settings, become moderately or severely depressed. Among patients with medically intractable complex partial seizures, 62% of have a history of depressive disorders, 38% of whom satisfy criteria for major depressive illness (Victoroff et al. 1990). The focus of this section is depression in epilepsy, referred to as interictal depression.

While the clinical presentation of interictal depression is similar to that of depression in patients without epilepsy, as many as one-third of patients with interictal depression present with atypical features. Some researchers have described recurrent affective syndromes that resemble dysthymia and can last for hours to weeks (Hermann et al. 1991). Others have reported presentations that include chronic dysthymia with anhedonia, fatigue, anxiety, irritability, low frustration tolerance, and mood lability with tearfulness (Kanner 2003b) and presentations characterised by changeable mood with dysthymic-like episodes mixed with brief euphoria, irritability, explosiveness, anxiety, paranoia, neurovegetative symptoms, self-injurious behavior, and distress. The rate of suicide in patients with epilepsy (especially in those with temporal lobe epilepsy) is four times higher than in the general population (Harris and Barraclough 1997). Risk factors for suicidality in epilepsy include a history of previous suicide attempts, family or personal history of psychiatric illness, and stressful life events (Robertson 1997b).

Since anti-epileptic drugs (AEDs) can induce both positive and negative mood changes, caution should be exercised in selecting AEDs for depressed patients with epilepsy. Treatment with phenobarbital, primidone, tiagabine, vigabatrin, and felbamate is commonly associated with the development of depressive symptoms. In contrast, carbamazepine, valproate, and lamotrigine have mood stabilising properties and can be used to manage depression. Reductions in the dosage of these agents have been associated with the development of depression.

The treatment of depression in epilepsy has been poorly studied. Only one randomized, double-blind trial has been published. This study, which was not placebo-controlled, found greater improvement in depression in patients with epilepsy who were treated with nomifensine than with amitriptyline (Robertson and Trimble 1985). Thus, the recommendations presented in this section are based on clinical experience. While antidepressants, especially tricyclic antidepressants (TCAs), may lower seizure threshold, practically speaking, in well managed patients, this concern is often more theoretical than actual. Nevertheless, maprotiline, bupropion, amoxapine, and clomipramine should be avoided in patients with epilepsy because of their effects on seizure threshold (Curran and de Pauw 1998).

Selective serotonin reuptake inhibitors (SSRIs) (e.g., citalopram, escitalopram, fluoxetine, paroxetine, sertraline) are preferred as initial treatments for depression in epilepsy. They are well tolerated and effective in patients with epilepsy and have the least effects on seizure propensity of currently available antidepressant agents (Kanner et al. 2000). Venlafaxine also appears to be effective and safe in patients with epilepsy (Kanner 2003a). TCAs are also well-tolerated (Blumer and Zielinski 1988). However, given the suicide risk posed by epilepsy, risks of TCA overdose make this class less desirable. Monoamine oxidase inhibitors (MAOIs) are also well-tolerated, but less easy to use because of required dietary restrictions, although the recently approved patch formulation

of selegeline may be an exception. To minimise the risk of inducing or worsening seizures, it is prudent to start with low doses of antidepressant medication, with smaller incremental increases until a satisfactory clinical effect or target effective dose is achieved.

Pharmacokinetic interactions between AEDs and antidepressant medications must be considered (McConnell and Duncan 1998). Phenytoin, carbamazepine, phenobarbital, primidone, oxcarbazepine, and topiramate have enzyme-inducing properties that can affect the metabolism of antidepressant medications. Conversely, fluoxetine, paroxetine, fluvoxamine, and sertraline inhibit cytochrome P450 enzymes and thus may affect levels of AEDs (e.g., sertraline can increases levels of phenytoin). Co-administration of MAOIs with carbamazepine can result in hypertensive crises, while combined use of fluoxetine and carbamazepine can result in serotonin syndrome (Dursun et al. 1993).

Electroconvulsive therapy (ECT) can be used to treat major depression in patients with epilepsy who do not respond to antidepressant medications or when more rapid treatment is needed because of suicide risk. ECT it is rarely a cause of status epilepticus or increased seizure frequency (Keller and Bernstein 1993).

STROKE

In 1921, Kraepelin described an association between depressive disorders and stroke in his patients. Since then, it has been generally accepted that mood disorders are a specific complication of stroke (Folstein et al. 1977), (Robinson et al. 1987), (Robinson et al. 1993) with depressive disorders the most common post-stroke psychiatric condition (Burvill et al. 1995). However, uncertainties remain about the causes and treatment of depression in patients who have had a stroke. Making a diagnosis of depression in patients who have had a stroke can also be complicated by brain damage and neurological deficits resulting from the stroke—for example, aphasia may make it difficult for clinicians to understand what patients are saying.

Major depressive disorder occurs in about 25% of acute stroke patients (Astrom et al. 1993; Robinson et al. 1983) and is indistinguishable from major depressive disorder in patient who have not had a stroke (Lipsey et al. 1986). Symptoms of depression in patients who have had a stroke, in addition to sustained depression, include lack of energy, self-doubt, poor concentration, anorexia, sleep disturbance, pessimism, and anhedonia; suicidal ideas are also not uncommon. Less severe clinical depressions (minor depression or dysthymic depression with fewer symptoms) may occur in another 20% of patients following stroke (Robinson et al. 1983), and have a poor prognosis (Robinson et al. 1984).

Given the severity and persistence of poststroke depressions and their adverse effects on rehabilitation, effective treatment is essential, whatever the location of the brain injury. Two randomized, placebo-controlled studies of the TCA nortriptyline and one such study of the SSRI citalopram have demonstrated the efficacy of these agents in the treatment of poststroke depression (Andersen et al 1994; Lipsey et al. 1984; Robinson et al. 2000). Based on the findings of these studies, a reasonable approach for the treatment of poststroke depression is to start with a trial of citalopram or nortriptyline. If citalopram is ineffective or is not tolerated, a trial of nortriptyline is warranted if there are no contraindications, and vice-versa. Nortriptyline is preferred over other TCAs because it usually causes less orthostatic hypotension, sedation, and anticholinergic effects than other TCAs and has an established range of effective serum levels. If the depression is accompanied by delusional ideas or if patients have persistent wishes for death or suicidal ideas, more aggressive treatment should be considered, such as augmentation of antidepressants with lithium or antipsychotics, ECT, or psychiatric admission.

PARKINSON'S DISEASE

Depressive symptoms were noted by Parkinson himself when he described a particular patient as "a previously sanguine man . . . now dejected and melancholic" (Mayeux 1990), and an association between depression and Parkinson's disease (PD) is now well established. Recent research has confirmed that depressive disturbances are common in PD, with the prevalence of depression in PD reported to be approximately 40%–50% (Slaughter et al. 2001). Slightly less than half of these patients have major depression, while a majority have milder depression (e.g., dysthymia, minor, and sub-syndromal depression). Unfortunately, depression is undetected by clinicians in over half of affected patients—likely because of overlap between PD itself and the syndrome of major depression (Shulman et al. 2002). The core features of major depression in PD include persistent and pervasive low mood, diminished ability to enjoy activities (anhedonia), and/or a decline in level of interest from the person's usual baseline (Marsh et al. 2005). Anxiety symptoms and comorbid anxiety disorders are also common in patients with PD and may precede the onset of depression (Menza et al. 1993).

There is little evidence upon which to base advice regarding treatment of mood disturbances in PD (Weintraub et al. 2005). In the presence of persistent that are at least moderately disruptive, use of antidepressant medications should be considered. However, clinical trials have been limited and have not fully supported use of antidepressants in these patients; there is also little evidence that one antidepressant is preferable to another in PD (Richard et al. 1997). Dosing strategies are similar to what is recommended in geriatric psychiatry: start low and go slow, until an effective target dose is reached. SSRIs are frequently used to treat depression in patients with PD and are generally are preferred as first line agents. However, TCAs are also often needed because they are sometimes more effective. If symptoms do not remit, it is important to increase the dose to a usual antidepressant target dose or switch to a different antidepressant. ECT is indicated when patients are severely depressed and have not responded to antidepressant medication or when patients are in danger of death from inanition or suicide; ECT can also be beneficial for motor symptoms of PD in the absence of a concurrent mood disturbance (Faber and Trimble 1991). Most patients with PD who have achieved a good response to treatment for depression will require chronic maintenance therapy because depressive symptoms often recur when medications are reduced.

TRAUMATIC BRAIN INJURY

Major depression is seen in about 25% of people with traumatic brain injury (TBI). Symptoms of depression seen in patients with TBI include persistent sadness, guilt, feelings of worthlessness, hopelessness, suicidal thoughts, anhedonia, and changes in patterns of sleep, appetite, and energy. These symptoms may also be associated with delusions and hallucinations. It should be noted that changes in sleep, appetite, and energy may be due to the brain injury itself, or to the noise, stimulation, or deconditioning associated with prolonged hospitalization in the early period after the injury. Poor social functioning before the injury and left dorsolateral frontal and/or left basal ganglia lesions have been associated with an increased probability that patients will develop major depression after a TBI (Jorge et al. 1993).

Pharmacotherapy options for post-TBI depression include antidepressants, psychostimulants, and ECT. SSRIs are the first choice antidepressants for these patients because they have the best side-effect profile. Second-line antidepressants include venlafaxine and mirtazepine. Medications with anticholinergic potential such as TCAs (e.g., amitriptyline, nortriptyline) and bupropion should be considered third line as they may worsen other brain injury symptoms. Psychostimulants (e.g., methylphenidate) and dopaminergic agents (e.g., amantadine) are often effective when used to augment antidepressants. ECT is highly effective for patients with TBI whose depression is refractory to antidepressants. Patients with TBI who have major depression and psychotic features often require antipsychotic medications (e.g., aripiprazole, olanzapine, quetiapine, risperidone, ziprasidone). Effective psychotherapy approaches in post-TBI depression include supportive therapy, interpersonal therapy, and cognitive-behavioral therapy.

MULTIPLE SCLEROSIS

Depression was among the first symptoms recognised as being associated with multiple sclerosis (MS) from its earliest descriptions. Jean-Martin Charcot (1825–1893), who provided the first accurate and comprehensive clinico-pathological description of MS, described severe depression in his first case presentation, Mlle. V., a 31-year-old woman who stopped eating and had to be fed by a stomach pump to keep her alive.

The point prevalence of major depression among clinic patients with MS is 15%–30%, with lifetime prevalence of major depression in patients with MS reported to be 40%–60% (Caine and Schwid 2002). This rate is three to ten times greater than the rate of major depression in the general population. Furthermore, depression is more common in MS than in many other chronic illnesses, including other neurologic disorders. It can be challenging to diagnose depression in MS using standard criteria because the somatic signs and symptoms associated with MS resemble some of the symptoms of depression. Debilitating fatigue that almost always interferes with a patient's activities is best considered a symptom of an underlying depression until proven otherwise. Suicidal ideation has a cumulative prevalence of 30% in patients with MS, while 6%–12% of patients with MS make a suicide attempt. This rate is 7.5 times the rate reported in the age-matched general population. One study reported that suicide was the third leading cause of death in patients with MS (Sadovnick et al. 1991).

In selecting antidepressants to treat patients with MS, clinicians should consider the side-effect profile of the medication and tailor it to the patient's specific symptoms. Bupropion, fluoxetine, and venlafaxine tend to be activating and may ameliorate fatigue; in contrast, desipramine, mirtazepine and paroxetine are sedating and stimulate appetite, effects that can be beneficial for patients with insomnia and anorexia. Antidepressant selection is also influenced by the opportunity to simultaneously treat comorbid conditions that are frequent in patients MS. For example, TCAs and duloxetine are good choices for patients with MS-associated neuropathic pain.

Studies of psychotherapy treatment in depressed patients with MS have examined cognitive-behavioral therapy (CBT) as well as relaxation and supportive group therapies. Psychotherapy that focuses on coping skills has been reported to be more effective than insight-oriented therapy in these patients. CBT has been shown to be effective in depressed patients with MS (Mohr et al. 2001). Empirical data also suggests that exercise is an effective adjunctive treatment for depression in MS, because it tends to improve mood, sexual function, pain, and fatigue.

OTHER NEUROLOGIC ILLNESSES

Depressive disorders may also occur in the context of less common neurologic illnesses (Table 2.1). Patients with neurological disorders who exhibit or complain of depressed mood and associated symptoms of a depressive disorder, as well as those with motivational or rehabilitation problems, should receive a therapeutic trial of an antidepressant medication. Silver et al. (1990) provide the following recommendations concerning psychopharmacology of depression in patients with neurological disorders:

- The choice of antidepressant should depend primarily on the side-effect profile of the agent; drugs with the fewest sedative, hypotensive, and anticholinergic side effects are preferable.
- Antidepressant plasma levels should be monitored if possible. If the patient becomes severely hypotensive, confused, or sedated, the medication dose should be reduced.
- Medication should be continued for at least 6 months after clinical improvement (i.e., after the depressive episode has abated).

TABLE 2.1

Depression in Less Common Neurological DIsorders

Disorder	Authors	Comments*	Treatment*
Huntington's disease (HD)	Di Maio et al. 1993a,b; O'Shea 1997	Depression is the most frequent psychiatric illness in 38% of patients with HD. Stressful life events (43.1%) can lead to misdiagnosis. Depression can appear before neurological signs. Depression can occur in a subset of families with HD. Suicide and deliberate self-harm are common.	Symptomatic patients should receive tetrabenazine + antipsychotics, clozapine (for psychosis), ECT if needed
Gilles de la Tourette's syndrome	Robertson et al. 1993, 1997a	Depressive disorder and anxiety more common than in controls. Co-occurring obsessive-compulsive phenomena also found.	Selective serotonin reuptake inhibitors (SSRIs) for depression or, in larger doses, for obsessive-compulsive symptoms
Wilson's disease (hepatolenticular degenerative)	Dening 1985	Psychiatric symptoms usually appear late, although they may precede neurological symptoms in 20% of patients.	Anticopper drugs: dimercaprol, penicillamine
Spasmodic torticollis	Jahanashahi and Marsden 1992	Depressive disorder is common; possibly as a consequence of abnormal posture.	Symptomatic improvement of depression with botulinum toxin locally injected
Myasthenia gravis	Rohr 1992	Psychiatric disorder seen in 20% of patients; younger families at risk	Tricylic antidepressants may worsen symptoms; use ECT and plasma exchange

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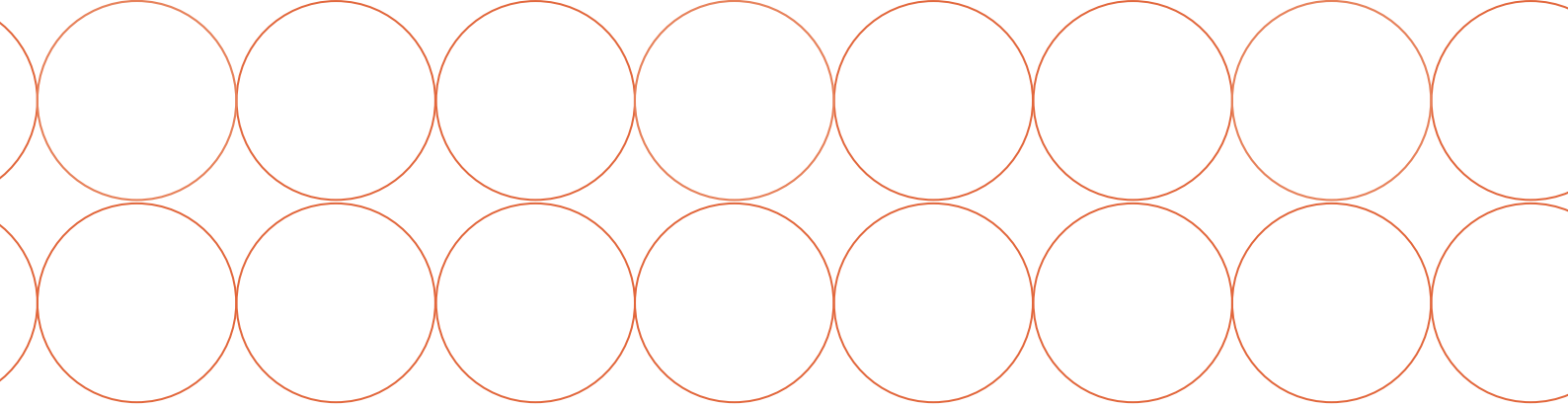

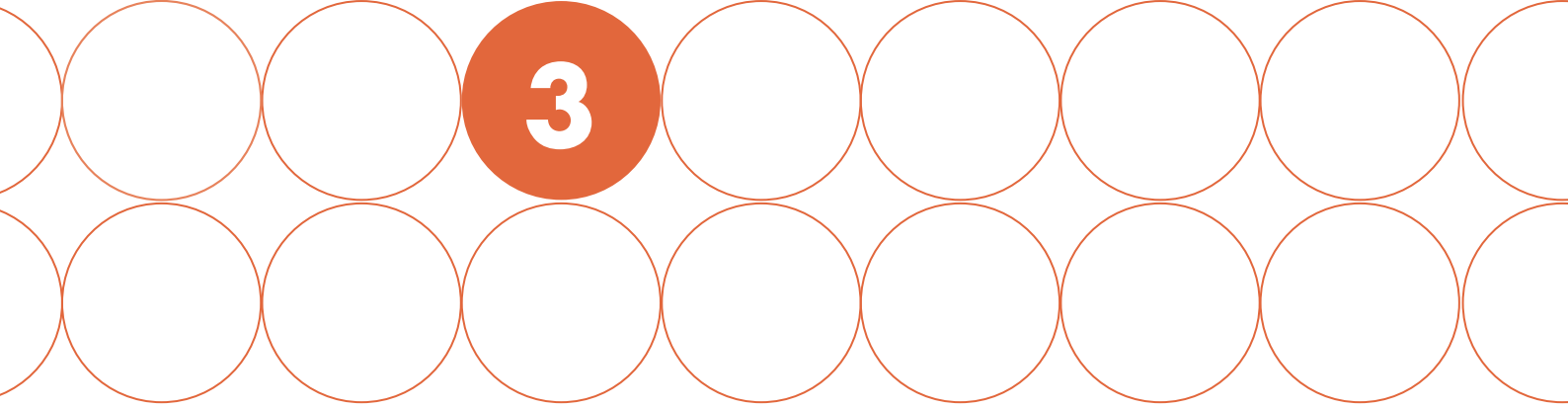

Chapter 3

Depressive Disorders and Cardiovascular Medicine

Lawson Wulsin, MD

Depression more than triples the chances that a person with a heart attack will die within the next 6 months (Glassman and Shapiro1998; Rudisch and Nemeroff 2003), yet few coronary care units or cardiologists screen for depression following a heart attack. Major depressive disorder occurs in 15%–30% of patients with acute coronary syndromes. In 1995, Frasure-Smith et al. reported that major depression in patients in the hospital after a myocardial infarction (MI) substantially increases the risk of mortality during the first 6 months. There is now consistent evidence that depressive symptoms predict long-term mortality following an MI (within the next 18 months) (Frasure-Smith and Lesperance 2003). Depression also triples the chances that a person with any chronic physical illness will fail to adhere to a treatment regimen over 3 months (DiMatteo 2000). A recent meta-analysis (van Melle et al. 2004) found that depression post-MI was associated with a 2- to 2.5-fold increased risk for all cause mortality and cardiovascular events. In addition, depression post-MI is a major cause of incomplete recovery (Ladwig et al. 1994), poor quality of life (Beck et al. 2001), delayed return to work (Söderman et al. 2003), non-adherence to treatment (Carney et al. 2005), and non-attendance at cardiac rehabilitation (Lane et al. 2001). It is estimated that approximately 1 of 5 patients has depression after an MI (Schleifer et al. 1989).

Since only about half of all people with depression receive any treatment, and only about a fifth get effective treatment, untreated depression often sabotages the management of chronic physical illnesses such as heart disease (Kessler 2003). Patients and the primary care clinicians who help them manage their chronic illnesses over many years need effective strategies to prevent depression from undermining their best efforts. Table 3.1 summarises some links that have been identified between depressive disorders and cardiovascular illness.

TABLE 3.1

Links between depressive disorders and cardiovascular illness

Depression exacerbates four of the six major risk factors for coronary disease: smoking, obesity, physical inactivity, and diabetes.	Depression exerts its effects on coronary disease through two pathways: 1) behavioral, and 2) neuroendocrine.	Behavioral links include poor adherence, low social support, high calorie diets, low physical activity, and substance abuse, especially smoking.	Neuroendocrine links include increased activity of the stress response system, autonomic imbalance, low heart rate variability, increased platelet aggregation, and increased vascular inflammation.	According to the "vascular depression" hypothesis, coronary disease may contribute to late-onset depression through its association with reduced or altered perfusion of key areas of the limbic system and frontal lobes.

DEPRESSIVE DISORDERS AS A RISK FOR CARDIOVASCULAR MORBIDITY AND MORTALITY

Depression independently raises the risk for both developing coronary disease (Rugulies 2002; Wulsin and Singal 2003) and for the progression of existing coronary disease (Wulsin 2004). Based on a review of 22 studies of outcomes after an MI, van Melle et al. (2004) reported that depression more than doubled all cause mortality (odds ratio 2.4) and cardiovascular mortality (OR 2.6) as well as the rate of cardiovascular events (OR 2.0). In a related review of 20 studies of outcomes of coronary disease, the cardiovascular mortality risk conferred by depression was greater at 2 years than at 6 months after the assessment for depression (Barth et al. 2004). Despite multiple methodological differences among studies, data from prospective, adequately powered, etiological and prognostic studies that used objective outcome measures and recognised indices of depression are remarkably consistent in supporting depression as a risk factor for both the development and worsening of cardiovascular disease (Frasure-Smith and Lesperance 2005).

Although mild depressive symptoms contribute significantly to increased mortality, the more severe the depression, the greater the mortality risk. This dose-response effect has been reported in numerous studies (Drago et al. 2007; Wulsin 2004). A study by van Melle et al. (2007) found that treatment for depression post-MI did not improve the long-term depression status or cardiac prognosis compared with usual care. However, some recent findings suggest that particular subtypes of depression post-MI may be specifically related to impaired prognosis. De Jonge et al. (2006a) reported that only somatic/affective symptoms (but not cognitive/affective or appetitive symptoms) were associated with a worsened cardiac prognosis. Other studies have found that only incident depressions post-MI (i.e., new onset depressions rather than chronic or recurrent depression) (De Jonge et al. 2006b; Grace et al. 2005) were related to poor cardiac outcome. Bush et al. (2001) reported that even minimal depressive symptoms increase mortality rates in patients post-MI (Bush et al. 2001).

Though fewer studies have examined the effect of depression on heart failure, the evidence points to a similar independent contribution of depression to the risk for death (Junger 2005; Vaccarino 2001), with a strong and graded association between severity of depressive symptoms and death 6 months later.

Little is know about the possible pathophysiologic mechanisms involved in the association between depression after acute MI and higher rates of morbidity and mortality. Various bio-behavioral mechanisms have been proposed to explain this association, including behavioral risk behavior (smoking, alcohol use, physical inactivity), poor adherence to treatment, elevated levels of pro-inflammatory cytokines, platelet activation, disturbances in the autonomic nervous system (reduced heart rate variability), hypothalamic-pituitary-adrenal axis dysfunction, and the stress associated with events related to heart disease (e.g., an acute MI) (Evans et al. 2005; Lett et al. 2004; Rudish and Nemeroff 2003).

CARDIOVASCULAR DISEASE AS A RISK FACTOR FOR DEPRESSIVE DISORDERS

About 20% of patients with coronary disease or congestive heart failure have major depression. Another 20% have at least 2 weeks of minor depression (2–4 symptoms) (Freedland et al. 2003; Glassman and Shapiro 1998; Rudisch and Nemeroff 2003). In two studies of patients in whom depression was detected after an MI, the depression was shown to have been present before the infarction in 30%–50% of the subjects. One of these studies found that previous depression was associated with an increased risk of later cardiac failure (Dickens et al. 2005). Psychological variables, such as demoralisation, irritable mood, type A behaviour, that have been identified from psychosomatic research and than translated into operational tools (e.g., Diagnostic Criteria for Psychosomatic Research) are frequently detected in cardiac patients (Rafanelli et al. 2007).

Anecdotal reports of first episodes of depression following the onset of heart disease are common and have led to the hypothesis that cardiovascular disease triggers the development of depression. However, few studies have examined rates of new onset depressive disorders after a cardiac event.

The vascular depression hypothesis proposes that impaired perfusion to the limbic system or relevant parts of the cortex may explain the development of depressive disorders in the context of peripheral vascular disease (Alexopoulos 2003). Several recent studies have found an alarmingly high rate of "silent strokes" in elderly depressed samples, suggesting silent diffuse vascular disease may be associated with new depressive syndromes (Baldwin and O'Brien 2002; Rao 2000).

Vascular depression (depression with a late onset in individuals over 50 years of age in the context of known cardiovascular disease) occurs equally in men and women, and it may be less responsive to standard antidepressant treatments.

ASSESSMENT

When told that their patients met criteria for a depressive disorder, only two-thirds of physicians agreed with the diagnosis and need for treatment. Although medical physicians were often quite accurate in their assessment of depression, they did not recognise persistent depression in nearly 40% of patients (Koening 2007).

Two screening questions can identify clinically depressed patients with over 80% sensitivity (Whooley et al. 1997):

During the past month, have you often been bothered by

1) feeling down, depressed, or hopeless?
   NO / YES
2) little interest or pleasure in doing things?
   NO / YES

A similar set of questions can identify patients with a history of depression:

In your lifetime, have you ever been bothered for most of 2 weeks by

3) feeling down, depressed, or hopeless?
   NO / YES
4) little interest or pleasure in doing things?
   NO / YES

If the patient answers "Yes" to any one of these questions, this justifies further inquiry to assess the type and severity of depression.

Initial screening of patients for depression can be done by primary care providers or clinical research co-ordinators with minimal training or by patients themselves using a self-administered assessment tool such as the Beck Depression Inventory (Beck et al. 1961), the Patient Health Questionnaire (PHQ-9) (Kroenke 2001), or the Inventory of Depressive Symptomatology, self-report version (Rush et al. 1986). Patients with complex psychiatric histories or evidence that the depressive disorder is complicating the cardiac disorder should be evaluated by a psychiatrist.

DEPRESSIVE DISORDERS AND HEART SURGERY

About 20% of coronary bypass patients report major depression within a month after the surgery, and depression is as strong a predictor of 1-year adverse cardiac outcomes as low ejection fraction, according to a prospective study of 309 patients who underwent bypass surgery (Connerney et al. 2001). Depression is not usually a contraindication to heart surgery, including transplantation. However, careful assessment and management of the depression is essential to reduce the chance that the depression will interfere with complex cardiac regimens. Psychological concerns in heart transplantation differ from those in other forms of cardiac surgery in two ways: 1) the special psychological situation caused by "living with a new heart," and 2) the need to be highly adherent to the recommendations of the medical team after the operation, particularly during the period of immunosuppression.

TREATMENT OPTIONS

In general, what is good for the heart is good for the brain. The essentials of comprehensive treatment for heart disease (e.g., exercise, stress reduction, fish oil or omega-3 supplements, reduced sympathetic nervous system activity) are consistent with comprehensive treatment of major depression. Other non-pharmacological treatments for depression, such as psychotherapy, light therapy, relaxation training, and electroconvulsive therapy, are effective and safe in people with

common forms of heart disease. As the relationship between depression and cardiovascular disease has been increasingly recognised, a number of trials have begun to examine the impact of pharmacological and non-pharmacological interventions in patients with cardiovascular disease. Table 3.2 summarises the goals, methods, and results of a number of the major trials in this area.

The Canadian Cardiac Randomized Evaluation of Antidepressant and Psychotherapy Efficacy (CREATE) trial was the first randomized controlled trial to evaluate the acute phase efficacy of a selective serotonin reuptake inhibitor (SSRI) antidepressant (citalopram) and a short-term form of psychotherapy (interpersonal psychotherapy) in the treatment of major depression in patients with cardiovascular disease. Although citalopram was found to be superior to placebo in this study, IPT was not found to be better than clinical management, the control condition with which it was compared, in reducing depression levels as assessed by independent clinical ratings or self-report (Lesperance et al. 2007).

The ENhancing Recovery in Coronary Heart Disease study (ENRICHD) evaluated the effects of cognitive-behavioural therapy on depression and cardiac prognosis (Berkman et al. 2003). Improvement in psychosocial outcomes at 6 months favoured the group receiving the intervention. However, after an average follow-up of 29 months, there was no significant difference in event-free survival between usual care (75.9%) and psychosocial intervention (75.8%).

The Myocardial INfarction and Depression-Intervention Trial (MIND-IT), a large trial that compared the effects of antidepressant treatment and usual care on long-term depression status and cardiac prognosis, found no significant difference in cardiac outcome or depression status between the intervention and the care as usual arms at 18-month follow-up (van Melle et al. 2007).

No common cardiac medication causes depression, and in general, people with depression and heart disease do not have to avoid any specific cardiac medications. The long-held misconception that beta-blockers such as propranolol or atenolol cause depression was based on sloppy science and has been refuted a number of times over the last few years (Ko 2002). Rather, beta-blockers are good for the depressed patient with heart disease if they reduce autonomic instability. The SSRIs in general, and sertraline and citalopram in particular, are safe and effective for the treatment of major depression in people with coronary disease (Glassman et al. 2002; Lesperance et al. 2007). The recent SADHART (Sertraline AntiDepressant Heart Attack Trial) investigation demonstrated that sertraline is safe and efficacious in depressed patients with ischemic heart disease; however, this study was underpowered to detect a difference between sertraline and placebo on mortality rates (Glassman et al., 2002).

Both the MIND-IT (van Melle et al., 2007) and the ENRICHD studies failed to show that depression treatment produced improvement of medical outcomes after acute MI. However neither study had sufficient statistical power to convincingly test this hypothesis (Carney and Freedland 2007). Therefore, available data are more than sufficient to justify developing and evaluating better treatments for depression in cardiovascular disease patients as well in those at risk for development cardiovascular disease (Frasure-Smith and Lesperance 2005).

Table 3.3 lists a number of commonly used antidepressants and issues relevant to their use in patients with cardiovascular disease. While the first generation of antidepressants has been shown to benefit the majority of patients with clinical depression, these older agents are associated with adverse effects that make them a poor choice for patients with coronary heart disease (Davidson et al. 2006). For example, tricyclic antidepressants may contribute to arrhythmias during the post-MI period and are contraindicated in patients with coronary disease or cardiac arrhythmias (Roose et al. 1994). Options for treating depression in patients with cardiovascular disease were improved by the introduction of the next generation of antidepressants, particularly the SSRIs, whose safety in coronary heart disease patients is superior to that of the tricyclic agents (Davidson et al., 2006). A few studies suggest that SSRIs may protect against heart disease (Sauer et al. 2003). Since the SSRIs may, to a mild degree, reduce the tendency to form clots, it is possible that they may

TABLE 3.2

Relationship between depression and cardiovascular disease: Recent trials

Study	Citation	Goal	Method	Results and conclusion
CREATE	Lesperance et al. 2007	Evaluate efficacy of citalopram and IPT in reducing depressive symptom in patients with CAD and MDD	284 patients; randomized, controlled, 12-week, parallel group, 2 x 2 factorial trial	Trial documented efficacy of citalopram administered in conjunction with weekly clinical management for MDD; no evidence of added value for IPT over clinical management
ENRICHD	Berkman et al. 2003	Evaluate whether treatment for depression can improve cardiac prognosis in patients with CAD	2481 patients post-MI; randomized clinical trial; individually tailored cognitive behavioral therapy intervention.	Psychological outcome better at 6-month evaluation in group receiving the intervention compared with control group, but effect did not persist.
MIND-IT	van Melle et al. 2007	Evaluate whether antidepressant treatment for depression post-MI improves long-term depression status and cardiovascular prognosis	2177 patients post-MI; multi-centre, randomised, controlled trial comparing intervention with care as usual	Active treatment for depression post-MI did not improve long-term depression status or cardiac prognosis compared with usual care
SADHART	Glassman et al. 2002	Investigate safety and efficacy of sertraline treatment for MDD in patients with CVD	369 patients; randomized, double-blind, placebo controlled	Sertraline can be safely used in patients with CVD but was not found to be statistically superior to placebo on HAM-D scores; trial was not powered to detect differences in morbidity and mortality

Legend: MDD: major depressive disorder; CVD: cardiovascular disease; CAD: coronary artery disease; interpersonal psychotherapy (IPT); MI: myocardial infarction

CREATE: Canadian Cardiac Randomized Evaluation of Antidepressant and Psychotherapy Efficacy

ENRICHD: ENhancing Recovery in Coronary Heart Disease

MIND-IT: Myocardial INfarction and Depression-Intervention Trial

SADHART: Sertraline AntiDepressant Heart Attack Trial

augment the blood-thinning or anti-clotting effect of aspirin, warfarin (Coumadin), or clopidogrel (Plavix). Venlafaxine, when taken at high doses (above 300 mg/day), may raise blood pressure. Mirtazepine may cause some patients to gain weight. Bupropion may initially worsen anxiety; however, it is the antidepressant of choice for depressed patients who want to quit smoking or avoid the sexual side effects of the SSRIs.

The likelihood that a patient will respond to an antidepressant diminishes as the number of cardiac risk factors increases; therefore, to achieve a good response to antidepressant treatment, the clinician may also need to reduce some of those risk factors as well as be persistent in trying to find the right combination of treatments (Iosifescu et al. 2005). Treatment strategies for depression in patients with cardiovascular disease need to be adapted for cardiac care patients and can be quite different from those used to treat depression in the general population (American Psychiatry Association 2000).

TABLE 3.3

Effects of specific antidepressants on heart disease

Medication	Cardiac effects	Treatment considerations
Serotonin Reuptake Inhibitors		
Citalopram (Celexa) Escitalopram (Lexapro) Fluoxetine (Prozac) Paroxetine (Paxil) Sertraline (Zoloft)	May reduce clotting	May need to reduce doses of other blood thinners
Miscellaneous		
Bupropion (Wellbutrin)		Smoking cessation
Venlafaxine (Effexor)	At doses > 300 mg/day, may increase blood pressure	Avoid high doses or monitor blood pressure in patients with high blood pressure
Mirtazepine (Remeron)	Weight gain	Avoid in patients with diabetes or obesity
Duloxetine (Cymbalta)		Possibly more effective than others for treatment of physical pain
Tricyclics		
Amitryptiline (Elavil) Nortryptiline (Pamelor) Imipramine (Tofranil) Desipramine (Norpramin)	Arrhythmias after heart attacks	Avoid in all patients with coronary disease or at risk for developing coronary disease

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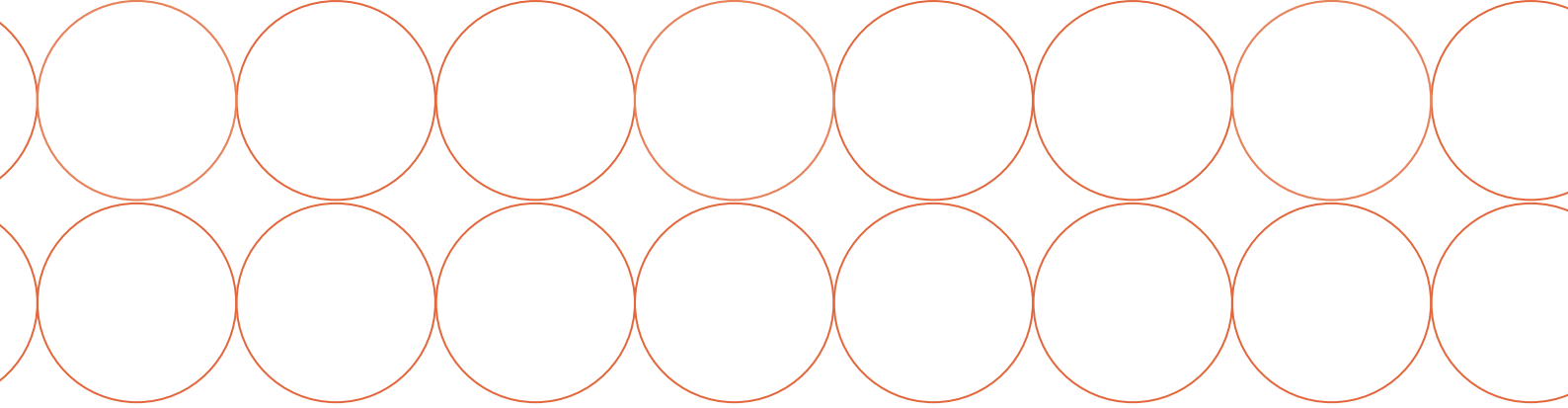

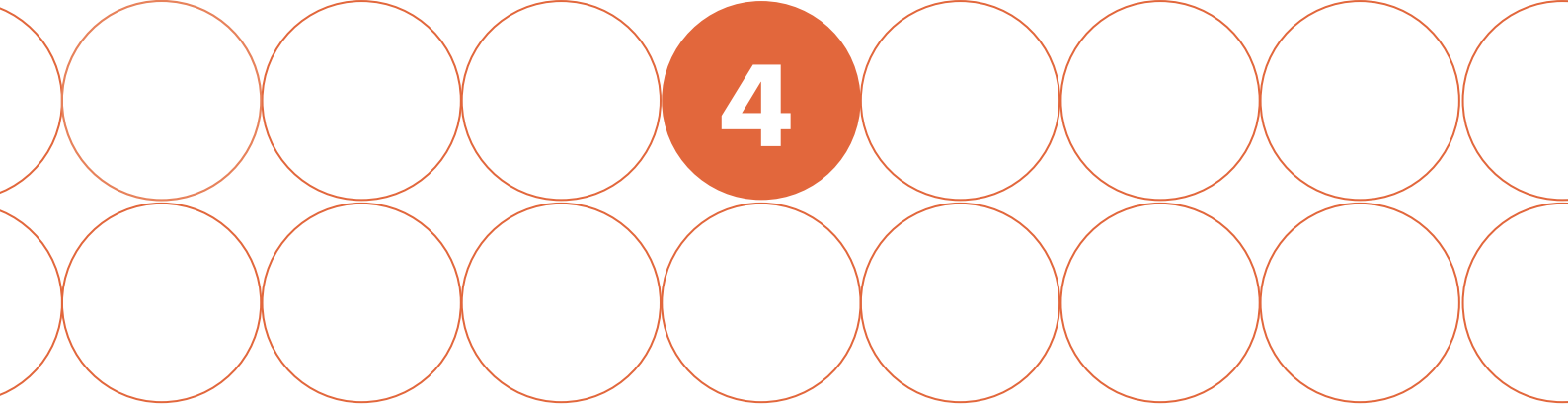

Chapter 4

Depressive Disorders in Obstetrics/Gynecology

This chapter focuses on women's experience of depressive disorders in relation to reproduction, including pre-menstrual syndrome, menopause, pregnancy, and related conditions.

Sheila Marcus, M.D.

PREMENSTRUAL SYNDROME (PMS) AND PREMENSTRUAL DYSPHORIC DISORDER (PMDD)

Many women throughout the world (Chandra et al. 1995) experience cyclical changes in physical and emotional symptoms pre- and perimenstrually (Bancroft 1993), although not all women are distressed by such symptoms, and few seek help. Approximately 50%–80% of menstruating women experience some mild premenstrual symptoms, about 20% report severe symptoms of premenstrual syndrome (PMS) that warrant treatment, and 3%–8% meet strict research criteria as specified in the *Diagnostic and Statistical Manual for Mental Disorders, 4th edition, text revision* (DSM-IV-TR, American Psychiatric Association 2000) for premenstrual dysphoric disorder (PMDD). (Deuster et al. 1999; Perkonigg et al. 2004; Wittchen et al. 2002). The hallmark features of PMDD include markedly depressed mood, anxiety, tension, affective liability, irritability, lethargy, food cravings, and physical symptoms such as breast tenderness or headaches. The DSM-IV-TR research criteria (Table 4.1) require that a woman experience 5 out of 11 of these symptoms during the late luteal phase, and that these symptoms interfere with social and/or occupational functioning.

A history of depressive disorders seems to increase a woman's vulnerability to depressive changes in the perimenstrual period (Bancroft et al, 1994), while cyclical variation of ovarian steroids (Bancroft 1993) and serotonergic dysregulation (Halbreich and Tworek 1993; Kouri and Halbreich 1997) seem to contribute to PMS. By contrast, cultural attitudes toward menstruation, cognitive style, neuroticism, personality, and a propensity for depressive illness seem to increase a woman's vulnerability for PMDD (Bancroft 1993). Assessment should include prospective daily ratings during at least two consecutive cycles. Women who fulfil criteria for PMDD should be differentiated from those with premenstrual exacerbations of a current depressive disorder. Treatment includes conservative interventions (such as lifestyle and stress management), cognitive-behavior therapy, suppression of ovulation (oral contraceptives may help, although they may also exacerbate symptoms in some patients), and antidepressants, which have been demonstrated to improve symptoms and quality of life in women with PMDD. In at least one study, ovulation suppressors produced a better response in the physical symptoms of PMDD but were less effective in treating severe premenstrual depression (Freeman 2005). In contrast, selective serotonin reuptake inhibitors (SSRIs) improve affective symptoms but have a more variable effect on somatic symptoms in PMDD (Halbreich et al. 2002). A recent, large epidemiological study found that some women with PMDD experienced positive mood changes while others experienced negative mood changes following institution of oral contraceptives. The authors concluded that oral contraceptives do not influence premenstrual mood in most women, and that premenstrual mood is most likely to deteriorate in women with a history of depression and to improve in women with early-onset premenstrual mood disturbance or dysmenorrhea (Joffe et al. 2003).

ORAL CONTRACEPTIVE USE

A twin study suggested that there may be a familial risk of developing depressive disorders during oral contraceptive use (Kendler et al. 1988). Some early studies reported an association between depressive disorders and the use of high-dose progestin oral contraceptives (Grant and Pryse-Davies 1968). Other studies found that users of oral contraceptives may develop a pyridoxine deficiency (Rose et al. 1972) and that depressive symptoms in this situation may benefit from pyridoxine supplementation (Adams et al. 1973). There appears to be some evidence that oral contraceptives have a salutatory effect on mood among women of all ages whose hormones are in a state of flux. A recent placebo-controlled trial showed improvement in scores on the Center of Epidemiological Studies Depression Scale (Radloff 1977) in adolescent girls treated with placebo or oral contraceptives (O'Connell et al. 2007). Some studies have examined the use of oral contraceptives among postpartum women and found a significant improvement in mood when estradiol was used for women with postpartum

TABLE 4.1

Research criteria for premenstrual dysphoric disorder*

A. In most menstrual cycles during the past year, five (or more) of the following symptoms were present for most of the time during the last week of the luteal phase, began to remit within a few days after the onset of the follicular phase, and were absent in the week postmenses, with at least one of the symptoms being either (1), (2), (3), or (4):

1. markedly depressed mood, feelings of hopelessness, or self-deprecating thoughts
2. marked anxiety, tension, feelings of being "keyed up," or "on edge"
3. marked affective lability (e.g., feeling suddenly sad or tearful or increased sensitivity to rejection)
4. persistent and marked anger or irritability or increased interpersonal conflicts
5. decreased interest in usual activities (e.g., work, school, friends, hobbies)
6. subjective sense of difficulty in concentrating
7. lethargy, easy fatigability, or marked lack of energy
8. marked change in appetite, overeating, or specific food cravings
9. hypersomnia or insomnia
10. a subjective sense of being overwhelmed or out of control
11. other physical symptoms, such as breast tenderness or swelling, headaches, joint or muscle pain, a sensation of "bloating," weight gain

Note: In menstruating females, the luteal phase corresponds to the period between ovulation and the onset of menses, and the follicular phase begins with menses. In nonmenstruating females (e.g., those who have had a hysterectomy), the timing of luteal and follicular phases may require measurement of circulating reproductive hormones.

B. The disturbance markedly interferes with work or school or with usual social activities and relationships with others (e.g., avoidance of social activities, decreased productivity and efficiency at work or school).

C. The disturbance is not merely an exacerbation of the symptoms of another disorder, such as Major Depressive Disorder, Panic Disorder, Dysthymic Disorder, or a Personality Disorder (although it may be superimposed on any of these disorders).

D. Criteria A, B, and C must be confirmed by prospective daily ratings during at least two consecutive symptomatic cycles. (The diagnosis may be made provisionally prior to this confirmation.

*Reprinted with permission from the American Psychiatric Association. Diagnostic and Statistical Manual of Mental Disorders, 4th Edition, Text Revision. Washington, DC: American Psychiatric Association; 2000:774.

depression. (Gregoire et al. 1996). Another randomised controlled trial found that estradiol enhanced mood in perimenopausal women (Soares et al. 2001). However, estradiol did not significantly improve mood in post-menopausal women with depression (Morrison et al. 2004; 2005) . A recent assessment of women under 40 years of age with major depressive disorder who participated in the STAR*D trial reported that those women who were taking progestin-only agents had more comorbid general medical conditions, hypersomnia, weight gain, and gastrointestinal symptoms than women taking combination agents or those who were not taking oral contraceptives. The women taking combined hormone contraception had fewer depressive symptoms as evaluated on the 16 item Quick Inventory of Depressive Symptomatology (Rush et al. 2003; Young et al. 2007). There is some suggestion that long-acting depot progestins (Norplant, Depo-Provera), may be more problematic for mood, particularly in women who are predisposed to depression, and have elevated mood scores when they initiate these medication (Westhoff et al. 1998a and b). The recent introduction of lower dose oral contraceptives may have led to a decrease in associated depressive symptoms.

MENOPAUSE

The prevalence of depressive disorders does not seem to increase during menopause (Hunter 1996), and depression is no more likely to occur during menopause than at any other time in a woman's life (Nolen-Hoeksema 1995). Rather, it is likely that the emergence of depression during midlife in women most often represents a recurrence or relapse of a previous episode. Some studies suggest that women with a history of mood symptoms accompanying alterations in reproductive hormones, such as those occurring during the postpartum and premenstrual phases, may be at particular risk for experiencing a major depressive disorder (MDD) during menopause (Hay et al. 1994). Negative beliefs about menopause and experiencing a longer than usual perimenopausal period (Avis et al. 1994) are associated with an increased risk of depressive disorders. In cultures with positive attitudes toward menopause, women tend to report few symptoms (Flint 1975). Psychosocial factors associated with depressive disorders at other stages of life, including stressful life events, lack of social support, past depressive disorders, and low socio-economic status, are also risk factors for depressive disorders during menopause (see also Volume I, Chapter 4). Life changes, particularly losses and other interpersonal role transitions, have been associated with the onset and maintenance of depression in women (Weissman et al. 2000). Other physiological changes such as insomnia, which may accompany the decline in estrogen during the transition to menopause, may predispose some women to changes in mood (Eichling and Sahni 2005). For women with prominent insomnia complaints, estradiol may play a role in stabilising sleep. Behavioural management and sleep hygiene as well as use of novel new agents such as zolpidem may provide short-term relief from insomnia and prevent further deterioration in mood symptoms. (Soares and Murray 2006). Although there is evidence of improved well-being in healthy women taking hormone replacement therapy (HRT) (Pearce et al. 1995), as discussed above, there is little evidence to suggest that HRT improves depressive disorders in menopausal women (Morrison et al. 2004). Thus, women who have depressive symptoms during menopause should be treated with conventional treatments, such as antidepressant drugs and psychotherapy. In contrast, HRT may reduce the likelihood of depressive disorders in women who have undergone a surgical menopause (Sherwin and Gelfand 1985).

PREGNANCY-RELATED DEPRESSION

At one time pregnancy was considered to have a "protective" effect in terms of depression, but it is now known that the risk of mood disorders during pregnancy (10%) is roughly equivalent to that in non-gravid women (Cohen et al. 1989), and it has been reported that up to 18% of women suffer from sub-syndromal depressive symptoms during pregnancy (Marcus et al. 2003). Sleep and appetite dysregulation are viewed as part of the normative experience of pregnancy, and the vast majority of women who experience depressive symptoms or MDD during pregnancy are under-treated (Marcus et al. 2005). Untreated MDD is an important risk factor for unfavourable pregnancy outcomes, including poor weight gain, difficulty obtaining prenatal care, and increased alcohol and drug use (Miller 1991). Studies have demonstrated that perceived stress associated with life events, as well as depression and anxiety, during pregnancy predicted lower birth weight, decreased Apgar scores, prematurity, and smaller head circumference in infants (Sandman et al. 1994; Steer et al. 1992; Zuckerman et al. 1990). In addition, there is a growing literature indicating that prenatal depression may have an impact on a number of neonatal outcomes, including infant neuroendocrine function (higher cortisol and lower dopamine and serotonin levels) and performance on neonatal behavioral assessments (Field et al. 2004, 2006; Lundy et al. 1999). Prenatal and postpartum depression may also have an impact on neonatal behaviours including sleep, feeding, and crying (Diego et al. 2004). The risk of suicide, is very low during pregnancy—as little as one-twentieth that seen in the general population (Appleby 1991). Risk factors associated with the development of depressive disorders in pregnancy are summarised in Table 4.2.

While pregnancy itself does not appear to substantially change the course of bipolar disorder, studies document high rates of bipolar relapse during pregnancy, when mood stabilisers are discontinued. (Viguera et al. 2002; Worley 2007a and b). Clinicians should keep in mind that completed suicide occurs in 10%–15% of the general population with bipolar I disorder and base decisions on a risk-benefit model that takes into account the health and well-being of both mother and fetus (Dell and O'Brien 2003; Worley 2007b).

TABLE 4.2

RIsk Factors for the development of depressive disorders in pregnancy

Higher number of previous pregnancies (O'Hara 1986)	Previous depressive disorders (Marcus et al. 2000)	Single marital status or marital conflict (Marcus et al. 2000)	Alcohol use during pregnancy (Marcus et al. 2000)	Bereavement in the second or third trimester (Kumar and Robson 1984)

Treatment of Depressive Disorders During Pregnancy

Treatment should be tailored to the severity of the depressive disorder, the risk of recurrence, and the wishes of the woman and her family. Research that has investigated interpersonal therapy (IPT) and cognitive-behavioural therapy (CBT) in the treatment of unipolar depression during the puerperium suggest positive outcomes when therapy is delivered by appropriately trained treatment providers (Cooper et al. 2003; O'Hara et al. 2000). For women who are reluctant to begin or continue pharmacotherapy, these psychotherapy treatments may be useful alternatives. Likewise, for women who choose to use pharmacotherapy, but have significant psychosocial stressors, these treatments may be essential augmentation strategies.

There is currently some scientific debate about the safety of some of the SSRIs during pregnancy. A great many early studies involving both the SSRIs and the TCAs suggested that neither class was likely to contribute to major congenital anomalies above the 1%–3% baseline risk seen in the general population of pregnant women (Addis and Koren 2000; Altshuler et al. 1996; Cohen et al. 2000; Ericson et al. 1999; Goldstein 1995; Nulman and Koren 1996). However, more recent studies suggest that first trimester exposure to SSRIs may contribute to preterm delivery and minor malformations (Chambers et al. 2006; Hendrick et al. 2003; Kallen 2004). Recent research also suggests that, like the older TCAs, the SSRIs may be associated with difficulties in neonatal adaptation, including irritability, hypertonicity, and feeding and sleep difficulties (Nordeng et al. 2001). Paroxetine was recently reclassified as a category D agent during pregnancy, in part due to a report from GlaxoSmithKline (GlaxoSmithKline 2005) suggesting that infants exposed to paroxetine during the first trimester had an increased risk of congenital malformations (4% vs. 2% in the general population), particularly cardiovascular anomalies (3% vs. 1% in general population). A recent meta-analysis confirmed these concerns about increased cardiovascular risk, but also noted that a detection bias might have contributed to the findings because of a 30% increased rate of ultrasound during pregnancy and 2-fold increased rate of echocardiograms in the neonates (Bar-Oz et al. 2007). Finally, Chambers, et al. (2006) have suggested that persistent pulmonary hypertension of the newborn may be associated with late trimester use of SSRIs.

Untreated bipolar illness poses a high risk for maternal morbidity and relapse during pregnancy and is a major risk factor for postpartum psychosis. This risk must be balanced with the potential risk for teratogenicity when mood stabilisers are used during pregnancy. Lithium has been linked to teratogenicity, especially cardiac malformations including Epstein's anomaly. While the absolute risk in lithium users is small (1–2:1000), it represents a relative risk that is 10- to 20-fold higher than the risk of this anomaly in the general population which is 1:20,000 (Cohen 2007; Pinelli et al. 2002). Lithium has also been linked to fetal renal and thyroid dysfunction. Women who take lithium after the first trimester may need higher doses as the pregnancy progresses because of changes in metabolic activity, fluid volume, and absorption rates; thus lithium levels should be carefully monitored. A screening ultrasound is indicated at 18 weeks. The drug should be reduced approximately 2 weeks before the expected date of delivery to prevent postpartum toxicity . After delivery, renal clearance changes rapidly, and lithium levels should again be carefully monitored to assure appropriate levels. Infants born to women using lithium may be predisposed to hypotonia and cyanosis during the neonatal period (Worley 2007b), but one follow-up study of 60 infants did not find neurodevelopmental or behavioural differences between infants exposed to lithium during pregnancy and their siblings who had not been exposed to lithium.

Anticonvulsant medications have also been reported to have substantial risk for producing anomalies in the fetus. Valproate increases the risk of major malformations and other serious pregnancy complications approximately fivefold if used within the first trimester. Neural tube anomalies have been reported in 7%–16% of pregnancies when valproate is used 17–30 days post-conception (Cohen 2007; Ernst and Goldberg 2002; Viguera et al. 2007; Worley 2007b; Wyszynski et al. 2005). The overall incidence of major malformations with valproate has been reported to be 11% (Kaneko et al. 1999). In women who are taking valproic acid during the first trimester, use of folic acid (4 mg/day) as well as vitamin B_{12} during both preconception and pregnancy is strongly recommended. Valproic acid is also associated with irritability, arrhythmias, feeding difficulties and changes in infant tone during the neonatal period (Jager-Roman et al. 1986; Kennedy and Koren 1998; Worley 2007b).

Lamotrigine has been approved for maintenance treatment of bipolar disorder. A recent analysis of birth outcomes from the Lamotrigine Pregnancy Registry found that, of 1,274 cases of pregnancies involving exposure to lamotrigine (with 441 receiving lamotrigine monotherapy), there were rates of malformation of 2.7%–5.6% (Viguera et al. 2007; Worley 2007b). The North American Epilepsy Registry has also implicated lamotrigine in an increased risk for cleft anomalies when used in the first trimester (Cohen 2007; U.S. Food and Drug Administration 2006; GlaxoSmithKline 2006; Worley 2007b).

Clinicians will often consider the use of an antipsychotic agent in the treatment of affective psychosis in pregnancy. Until recently, literature regarding the use of antipsychotics during pregnancy was confined to data on conventional agents. A recent meta-analysis (Altshuler et al. 1996) noted a slight increase in teratogenicity with low potency antipsychotics used in the first trimester. Additional research has examined older higher-potency antipsychotics agents such as perphenazine and haloperidol, with reassuring results in terms of safety (Altshuler et al. 1996; Miklovich and van den Berg 1976; Slone et al. 1977; Waldman and Safferman 1993).

Studies of newer atypical antipsychotics are ongoing, but, as yet, none of these studies have adequate power to confirm the presence or absence of teratogencity beyond the baseline rate. One study that examined 96 cases of olanzapine treatment in pregnancy found rates of fetal loss and prematurity that were within the range of normal controls, although one case of kidney dysplasia and one case of Downs syndrome were reported. Approximately 10% of infants born to women who were treated with clozapine have been noted to have major or minor anomalies or perinatal complications (Waldman and Safferman 1993); however, this study was considered insufficiently powered to make definitive suggestions about teratogencity per se.

Information concerning aripiprazole, quetiapine, risperidone, and ziprasidone is largely confined to findings obtained in animal studies and case reports. One postmarketing study examined outcomes for 9 women who took risperidone during pregnancy and found one case of corpus callosum; again this study was clearly of insufficient size to draw any conclusions regarding teratogenicity (Federenko and Wadhwa 2004).

Several case reports have documented transient extrapyramidal symptoms in neonates exposed to antipsychotic medications in utero (Auerbach et al. 1992). Only limited data are available concerning long-term developmental risk associated with the use of antipsychotic agents during pregnancy.

If a woman is severely depressed or when psychotic symptoms are present, ECT should be considered. There is little evidence to suggest that the procedure has excessive risks of adverse effects for fetus or mother. However, ECT may precipitate premature labour or antepartum hemorrhage and, thus, in addition to the usual safety procedures, external fetal heart monitoring should be used during and for a short time after each treatment.

Postnatal Depressive Symptoms (Maternity Blues)

Approximately 50%–75% of women experience minor mood disturbances in the first week following delivery, including mild "highs" or depressive swings (Glover et al. 1994). Although the "maternity blues" have been linked to a fall in the pre- to postnatal plasma estriol concentration (O'Hara et al. 1991) and in progesterone concentration (Harris et al. 1994), there are as yet no convincing physiological explanations for these mood changes. The blues do not need any specific treatment other than reassurance and explanation, but if they last longer than 2 weeks, diagnosis of a depressive disorder should be considered.

Postnatal Depressive Disorders

Postnatal depressive disorders affect 10%–15% of childbearing women (O'Hara and Swain 1996). There is a threefold risk of a depressive disorder in the month following childbirth, compared with monthly incidence rates in non-childbearing women (Cox et al. 1993). Rates of relapse are particularly high in women with a history of previous depression, with estimates ranging from 25%–50% (Wisner et al. 1996). Just as during other phases of life, the risk of depression during the postpartum period is influenced by genetic vulnerability. Other risk factors for postnatal depression include previous depression, single marital status, poor health functioning, alcohol use during pregnancy, and lower socio-economic status (Marcus et al. 2000). Risk factors associated with the development of postnatal depressive disorders are summarised in Table 4.3. Incidence rates for postnatal depression are similar across cultures, despite great cross-cultural variance in the customs and rituals surrounding childbirth (Kumar 1994). A postnatal depressive disorder is therefore one of the most common complications of childbearing and has potentially serious long-term adverse consequences for the mother, her family, and the developing child. Yet up to 50% of cases of postnatal depressive disorders are not detected (Briscoe 1986). Bipolar illness is associated with high rates of postpartum relapse (67%–82%) in the 3–6 months postpartum, with up to 20% of these women experiencing postpartum psychosis (Viguera et al. 2002; Worley 2007b). This risk is decreased by 2–5 fold when appropriate lithium prophylaxis is administered

Psychological and social factors are important correlates of postnatal depressive disorders. Problems in early parental relationships, marital problems, adverse life events, a family or personal history of depressive disorders, previous postnatal depressive disorders, and ambivalence about the pregnancy are the most commonly found concomitant factors (Kumar 1994). Cultural phenomena can give rise to particular risk factors. For example, in the Indian culture, sons are so desired that postpartum depressive disorders have been observed more commonly following the birth of girls than boys (Guzder and Meenakshi 1991). Sociocultural factors may influence the diagnosis and duration of postnatal depressive disorders; nevertheless, an isolated mother without family support is at risk of a depressive disorder, regardless of her cultural background (Cox 1996).

TABLE 4.3

Risk Factors for the development of postnatal depressive disorders

Family or personal history of depressive disorders	History of previous postnatal depressive disorders	Ambivalence about pregnancy	Recent life events (e.g., bereavement)	Marital problems	Lack of social support

Clinical Features

Postnatal depressive disorders are similar to clinically significant, nonpsychotic depressive disorders in terms of symptomatology, course, duration, and outcome. As in other depressive disorders, cultural factors may influence symptoms and their expression. One study comparing indigenous Caucasian mothers and Asian immigrants from India or Pakistan found no differences in their somatic and psychological symptom profiles. However, when reasons for a physician consultation were examined, it was found that the Asian women consulted exclusively for somatic symptoms, whereas Caucasian mothers were more likely to present with low mood (Upadhaya et al. 1989).

The depressed mother, regardless of origin, may be unable to care effectively for her baby, feel excessively concerned about the baby's health, or feel guilty that she is not coping. Behavioural difficulties in the baby or failure to thrive may be the first indication of a mother's depressive disorder. Women with severe depressive disorders may be at risk of harming themselves or the baby.

Postnatal depressive disorders are also associated with deterioration of the marital relationship and may lead to impairment of the psychological health of the partner (Ballard and Davies 1996). A growing body of evidence also suggests that a mother's depressive disorder has adverse effects on the infant, including impaired cognitive functioning, attachment difficulties, and behavioural problems. Deficits in cognitive development at 4 years of age have also been seen, particularly in boys of mothers from lower socio-economic backgrounds who have depressive disorders (Murray and Cooper 1997).

Treatment

As during pregnancy, the transition to motherhood may be challenging for many women. Both IPT and CBT are treatments that have demonstrated efficacy during the postpartum period (O'Hara et al. 2000). For women who have unique needs related to inadequate housing, finances, or support system, the services of a care manager, who can help the woman access resources and entitlements may prove helpful. The role of family or other support systems in helping women with the infant's overnight feedings cannot be over-emphasised. One of the best pieces of advice to give depressed women who have recently given birth is to get sleep at night in order to re-establish their proper circadian rhythm—achieving this will often require the help of a significant other. Resumption of physical activity as postpartum healing permits and maintaining adequate nutrition also facilitate recovery from depression

The finding that there was an overall increase in depressive symptoms in thyroid antibody-positive women who were followed for up to 8 months postpartum reinforces an association between thyroid disturbance and early-onset postpartum depressive disorders, highlighting the need to check thyroid function in postpartum women complaining of mood disturbance (Harris et al. 1992). Although estrogen has been found superior to placebo in treating postnatal depressive disorders (Gregoire et al. 1996), there is no evidence that women suffering from such disorders have progesterone or estrogen insufficiency. Preliminary research indicates that transdermal estrogen can also be an effective treatment in cases of severe postnatal depression (Gregoire et al. 1996). However, the relatively hypercoagulable state of women during the postpartum period places women at risk for thromboembolism when estrogen is used as a treatment during this time.

Randomized controlled trials have found that the SSRIs are effective in treating postnatal depressive disorders (Appleby et al. 1997). Recent research suggests that virtually all medications taken by women are secreted into the breast milk. Concentrations vary enormously and are dependent upon medication dosing relative to milk production, and whether the foremilk or the hindmilk is sampled (Stowe et al. 2000). SSRIs are commonly used by lactating women. Sertraline has been particularly well studied in lactation, with no ill effects reported in the majority of infants, although there have been rare case reports of hypertonia and irritability. In women using

fluoxetine while lactating, there are reports of infant colic and one report of a febrile reaction in the nursing infant. Use of mood stabilisers during lactation are somewhat more problematic and lactating women should general avoid lithium during lactation due to the remote chance of dehydration and lithium toxicity developing in the infant. The American Academy of Pediatrics considers the use of valproic acid "compatible" with nursing; however rare adverse effects have been observed in nursing infants. Studies to date of the newer antipsychotic agents have been insufficiently powered to draw any firm conclusions about their use during lactation.

Women who are severely depressed and at risk of harming the baby or themselves need extra support from family and health services and may require admission to hospital. Protective services may also be required in women whose capacities are so limited that they are unable to care for their children. Family and community support services and respite care may be provided by protective services in such cases. Most postnatal depressive disorders may be self limiting but nonetheless should be treated. Longitudinal studies show that about one quarter of affected mothers are still depressed at the child's first birthday (Kumar and Robson 1984).

Postpartum Affective Psychosis

The incidence of postpartum psychosis ranges from 1:500 to 1:1000 live births across cultures—a rate that has remained broadly the same for 150 years (Kumar 1994). Studies in Scotland have shown that a woman is 16–20 times more likely to require psychiatric admission in the first 3 months postpartum than in an equivalent time period prior to conception; in primigravidae, the risk is increased 35-fold in the first month postpartum (Kendell et al. 1989). Women with a history of bipolar disorder or puerperal psychosis are at particularly high risk for postpartum psychosis, with reports of the incidence in these women ranging from 1:3 (Kendell et al. 1989) to 1:2 (Marks et al. 1992). Biological factors are more important than psychosocial or obstetric factors in the etiology of postpartum psychosis. A family history of affective psychosis increases the risk, suggesting a genetic role (Brockington et al. 1982). Sudden fluctuations in hormone levels following labour may precipitate psychosis in genetically vulnerable women, possibly by leading to changes in neurotransmitter activity. Most patients present within 2 weeks of delivery as severe cases of psychosis, often accompanied by perplexity or confusion (Kendell et al. 1989). Suicidal and infanticidal ideation may occur.

Some women can be managed at home, but most require hospital admission (Oates and Gath 1989). When mother and baby are admitted together, all contact between the two should be supervised by staff to ensure the safety of the baby. Antidepressants, atypical antipsychotics, mood stabilisers, and ECT are used when appropriate, as in the treatment of postnatal depressive disorders. As noted above, while research regarding the use of antipsychotic medications during lactation is emerging, the available evidence is insufficiently powered to draw any firm conclusions about the use of these agents in nursing infants.

The prognosis for postpartum psychosis is good; with high response rates to adequate treatment trials. However, relapse can occur, so women should be closely monitored after returning to their homes. Women of childbearing age with histories of bipolar disorder should be advised of the risk of postpartum psychosis and monitored very closely postpartum. Recent data suggests that continuation of lithium during pregnancy may significantly decrease rates of postpartum relapse of bipolar illness (Blehar et al. 1998; Viguera et al. 2000).

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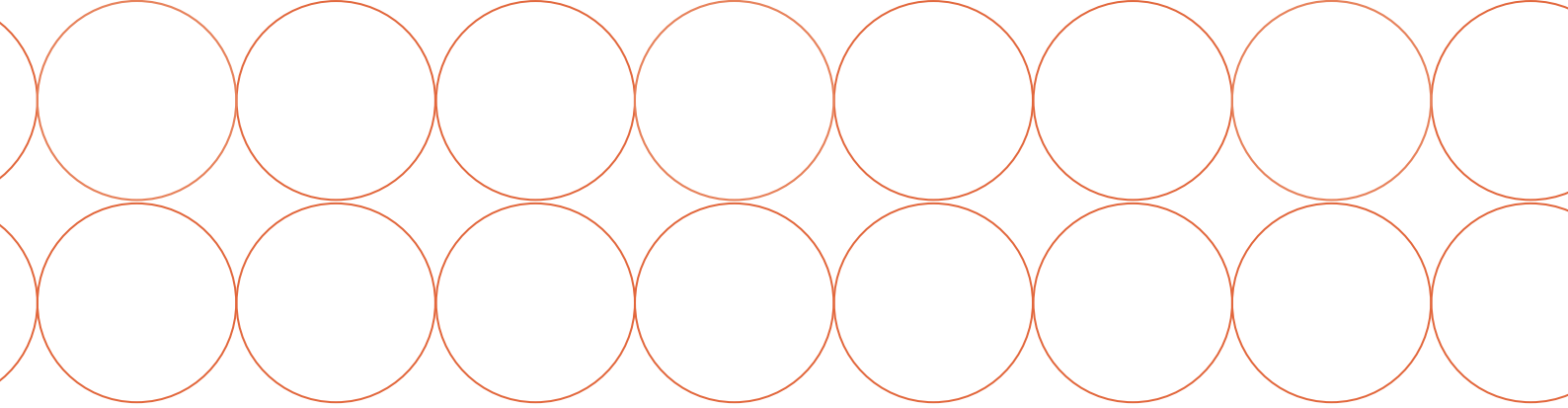

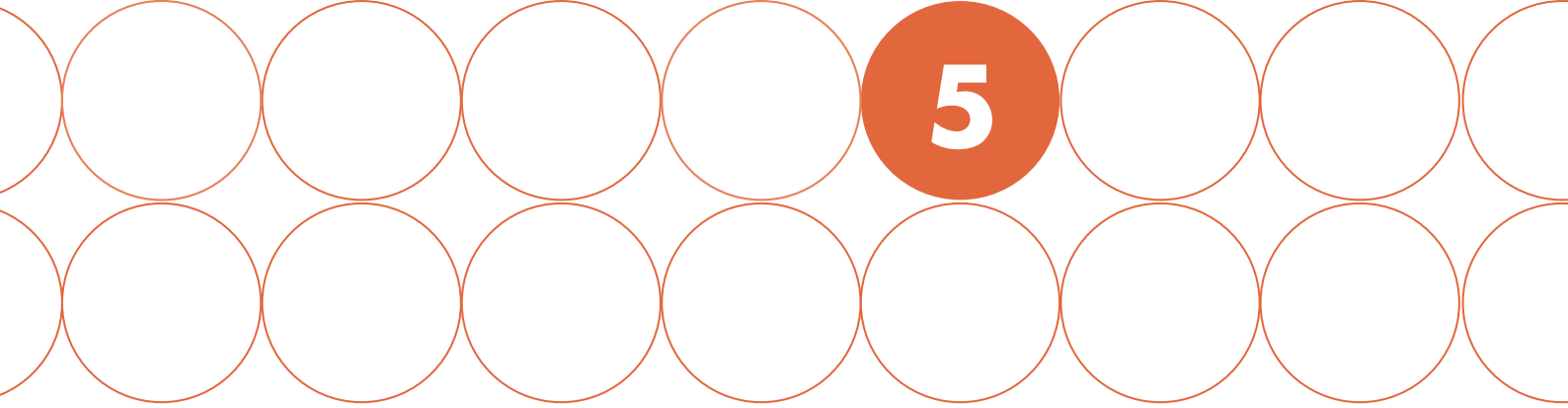

Chapter 5

Depressive Disorders in Patients with Endocrinological Disorders

Professor Stanislav Ivanov

INTRODUCTION

Cushing and Addison were among the first to observe depressive symptoms occurring in patients in the course of endocrine disease, and their findings were documented in subsequent studies. Excessive levels of hormones (or the absence of hormones), especially adrenal steroids and thyroid hormones, may cause depressive disorders, either directly or via mediation by neuropeptides (Fava et al. 1987).

In addition to following the recommendations for the general management of depression presented in Volume I, the clinician should monitor mood fluctuations in patients with endocrine disorders throughout the course of their illness. These patients may be at increased risk for "suicide by default"—that is, the deliberate refusal of therapeutic, dietary, and other measures necessary to sustain life or prevent deterioration, which masks a depressive illness. An example of this would be diabetic patients who stop taking their insulin (Fava et al. 1987). Sleep and appetite disturbances are often seen in endocrine disorders, but their presence does not discriminate between patients with and without depressive disorder. However, a diminished ability to think and indecisiveness are significantly more likely to be found in patients with endocrine disorders who also have depressive symptoms.

Dietary restrictions in patients with diabetes, impotence in men with hyperprolactinemia, and the disfigurement associated with disorders such as acromegaly may evoke feelings of tension, hostility, restlessness, or apathy in the patient and, in many cases, may also elicit aversive social responses (Lipowski 1985). Any or all of these reactions may set the stage for the development of depressive disorders.

CUSHING'S SYNDROME

Depressive symptoms tend to occur before the physical manifestations of Cushing's syndrome, with irritability a prominent feature in 86% of patients (Starkman et al. 1981). Cushing's syndrome may be misdiagnosed as treatment-resistant depression. Steroid inhibitors, such as metyrapone, may be more effective than antidepressants in treating depressive symptoms in patients with Cushing's (Jeffcoate et al. 1979). In the majority of patients, depressive symptoms resolve after treatment of Cushing's syndrome.

DIABETES MELLITUS

Diabetes mellitus is the most common endocrine disorder, with a prevalence of 1%–2% in the general population. The rate of depressive disorders in patients with diabetes is 9%–27%, compared with 4% in the community, and it has been reported that up to 40% of patients with diabetes have clear and persistent depressive symptoms (Anderson et al, 2000; Goodnick 1997). Depression in patients with diabetes is associated with a number of factors, including but not limited to the distressing somatic and social consequences of the illness. The hypothesis has been proposed that depression and diabetes may share a number of pathogenic factors, including hyperactivity of the hypothalamic-pituitary-adrenal (HPA) system, tissue hypoxia, genetic abnormalities, and auto-immune processes.

It is important to note that patients with diabetes and depressive disorder are less likely to comply with important aspects of diabetes treatment care, including ongoing monitoring of glucose values, exercise regimens, diet, medications and dose adjustments, monitoring of symptoms and potential complications, and ongoing contact with health care providers (Ciechanowsky et al. 2000; DiMatteo et al. 2000; Robertson, 1997). Depression has been found to have a significant negative impact on diabetes outcome and is associated with a 2.5-fold higher risk of macrovascular complications, an 11-fold higher risk of microvascular complications, and a 5-fold higher level of mortality (Black et al. 2003).

Major depressive disorders generally precede diabetic symptoms in patients with non-insulin-dependent diabetes mellitus (NIDDM) and, as is the case for other medical illnesses, they may actually increase the risk for onset of NIDDM (Eaton et al. 1996). Moreover, some data from large epidemiological studies suggest a positive correlation between severity of depression and risk of type 2 diabetes. Moderate and severe depressive symptoms are associated with a 2-fold increase in the risk of developing type 2 diabetes (Kawakami et al. 1999); the risk of type 2 diabetes increases to over 60% in the most severely depressed patients (highest quartile of depressive symptoms) (Golden et al. 2004). In contrast, depressive disorders tend develop after the onset of diabetes in insulin-dependent diabetes mellitus (IDDM), (Lustman et al. 1988), and the extent of hyperglycaemia correlates with the severity of the depressive disorder (Robertson 1997).

Clinical presentations of depressive disorders in patients with diabetes include major depression, dysthymia, and somatogenic depression, which have been found in 59%, 26%, and 15% of depressed patients with diabetes, respectively (Surkova et al. 2003; Zakharchuk 2005). Dysthymic disorder is more prevalent in patients with type 2 diabetes and usually manifests after the onset of diabetes. Major depression and somatogenic depression are found in relatively equal proportions in patients with types 1 and 2 diabetes. Somatogenic depression tends to occur in patients with the most severe diabetes (e.g., a long history of diabetes of more than 10 years and a high frequency of acute and chronic complications, diabetic comas, and ketoacidosis) and is characterised by significant asthenic symptoms (Surkova et al. 2003; Zakharchuk 2005).

In diagnosing depression in patients with diabetes, clinicians need to be aware that the two disorders share a number of symptoms (Figure 1). These overlapping symptoms require special attention from physicians because of the risk of "over-evaluating" the actual severity of the diabetic symptoms in cases in which the symptoms are completely or partly associated with underlying depression. The identification of "pure" somatic symptoms associated with depression can be helpful in recognising and monitoring depression in patients with diabetes (Surkova et al. 2003; Zakharchuk 2005).

When treating depressive symptoms in patients with diabetes, it is important to keep in mind that noradrenergic antidepressants (e.g., tricyclic antidepressants [TCAs], venlafaxine) increase insulin resistance and can worsen diabetes. On the other hand, the selective serotonin reuptake inhibitors (SSRIs) reduce insulin resistance and contribute to better control of diabetes (Goodnick 1997).

NEUROHUMORAL THEORIES OF DEPRESSIVE ILLNESS

Research on the pathogenesis of depressive disorders in Cushing's syndrome triggered a corollary line of investigation into the neuro-humoral basis of depressive illness. These investigations suggest that endocrine and psychiatric disorders share common etiological mechanisms. As early as the 1960s, Sachar (1967) reported increased HPA activity in depressive disorders, expressed by increased basal cortisol secretion, high urinary-free cortisol, and disrupted circadian periodicity. Further studies using the dexamethasone suppression test (DST), introduced by Liddle in 1955 as a diagnostic test for Cushing's syndrome (Liddle 1960), showed high rates of DST nonsuppression in depressed patients—particularly those with biological and psychotic features. This led Carroll to introduce the DST as a specific test for the diagnosis of melancholia (Abou-Saleh 1985, 1988). Some recent data suggest that the DST test may have a role in prediction of suicidal behaviour in depressed patients (Coryell and Schlesser 2001).

Reus (1984) provided a psychosomatic framework for a pathological continuum that ranged from depressed patients with abnormal and excessive levels in the HPA system due to intermittent or transient Cushing's syndrome to those with diencephalic Cushing's syndrome. Fava (1994) proposed a two-stage model for the pathogenesis of major depressive disorders and pituitary-dependent

FIGURE 5.1

Depressive somatic symptoms in DM patients

Sources: Surkova et al. 2003; Zakharchuk 2005

Cushing's disease. Stage 1 predominates and is common to both disorders; in this stage, stressful life events increase the secretion of corticotropin-releasing factor (CRF), resulting in biogenic amine neurotransmitters, leading to intracellular changes at the pituitary and adrenal hormonal levels. In stage 2, major depressive disorders and Cushing's syndrome manifest with HPA activation, which is reversible in depressive disorders but irreversible in Cushing's syndrome.

ADDISON'S DISEASE

As in Cushing's disease, depressive symptoms may precede the manifestation of Addison's disease, and the pathogenesis of depressive disorders may be related to increased secretion of CRF and adrenocorticotropic hormone (ACTH) and to imbalances in biogenic amine neurotransmitters induced by a lack of glucocorticoids. Adrenocortical insufficiency due to any cause is associated with a higher risk of major depression, although the prevalence of affective disorders and depression in patients with Addison's disease is more than 2 times higher than in patients with other forms of adrenocortical insufficiency (e.g., patients with osteoporosis) (Thomsen et al. 2006). Treatment with steroid replacement brings about rapid improvement in symptoms in mild-to-moderate cases; in more severe cases, ECT is an appropriate treatment.

HYPERTHYROIDISM

Kathol and Delahunt (1986) reported a 30% prevalence of major depressive disorders and a 40% prevalence of anxiety disorders and panic attacks in patients with hyperthyroidism. The pathogenesis of psychological symptoms in these patients may be related to the neuromodulating role of thyroid hormones and their effects on the alpha-adrenergic receptor response to catecholamines (Whybrow and Prange 1981). An excessive level of thyroid hormones may contribute to a state of tense dysphoria, whereas thyrotropin-releasing hormone (TRH) functions as an endogenous ergotropic substance in the brain, inducing behavioral effects indicative of increased arousal. Stressful life events may also contribute to the etiology of hyperthyroidism (Winsa et al. 1991).

Most depressive symptoms resolve with thyroid suppressing therapy and normalisation of thyroid function; in severe cases, antidepressant therapy or ECT may be needed. Psychotherapy is generally not effective in the treatment of depression associated with hyperthyroidism (Kleinschmidt et al. 1956).

An early study by Lahey (1931) described a condition called apathetic hyperthyroidism, in which the typical manifestations of increased thyroid activity are absent; instead, the patient presents with apathy, cardiovascular symptoms, and a depressive disorder. In this situation, depressive symptoms improve with treatment of thyrotoxicosis but respond poorly to antidepressants.

HYPOTHYROIDISM

Depressive symptoms, paranoid disorders, and dementia are commonly seen in hypothyroidism and often precede the physical manifestations of the disorder. Depressive disorders also occur in hypothyroidism secondary to thyroidectomy, thyroiditis, and probably lithium treatment (although this may be reversible once lithium is discontinued). About 10% of depressed patients

show some degree of hypothyroidism, which is often sub-clinical and may be detected only by TRH testing. Symptom-free auto-immune thyroiditis may underlie the sub-clinical hypothyroidism that may occur in patients treated with lithium and in women during the postpartum period, thus contributing to the increased risk of depressive disorders in these patients (see Volume II, Chapter 4 for a more detailed discussion of postpartum depressive disorders).

Depressive symptoms associated with hypothyroidism may not respond to thyroid replacement therapy and often require antidepressant medication. For treatment-resistant depressive disorders, including rapid-cycling bipolar disorder, thyroxine or triiodothyronine can be used adjunctively with antidepressants; these medications should be introduced gradually, in low doses, to avoid inducing cardiovascular problems or medication-induced psychoses.

PARATHYROID DISORDERS

Depressive symptoms in parathyroid disorders are often related to hypercalcemia or low magnesium. Symptoms tend to resolve within weeks after the correction of the calcium/magnesium imbalance; in some cases, antidepressant medication may be required.

Hypoparathyroidism, which often occurs after thyroidectomy, is associated with anxiety, irritability, and confusion in one third of patients. Fourman et al. (1967) reported a 40% prevalence of moderately severe depressive symptoms in patients with hypoparathyroidism; these symptoms improved after calcium was administered.

HYPERPROLACTINEMIA

Hyperprolactinemia, which is characterised by a decrease in libido, is often associated with anxiety and depressive disorders. Childhood neglect and abuse, which have been found to predispose individuals to depressive disorders in general, can also predispose to this endocrine disorder (Fava et al. 1987). Women with hyperprolactinemic amenorrhea tend to report significantly more depressive symptoms, hostility, and anxiety, compared with healthy women or those with amenorrhea but normal prolactin levels (Fava et al. 1987). Men with hyperprolactinemia also show more depressive symptoms compared with controls; however, the degree of depressive symptomatology is similar to that seen in patients with other medical disorders. These findings suggest that the behavioural correlates of hyperprolactinemia may depend on interactions with gonadal hormones.

Some studies suggest that postpartum women with high prolactin levels show more hostility compared with nonpostpartum women with normal prolactin levels. However, Abou-Saleh and colleagues (unpublished data, 1997) have shown an association between postpartum depressive symptoms, low prolactin levels, and low prolactin/progesterone ratio, compared with nonpostpartum, nondepressed women (see Volume II, Chapter 4 for a more detailed discussion of postpartum depressive disorders). Depressive disorders in patients with hyperprolactinemia do not respond well to antidepressant medication. However, when bromocriptine is given to reduce prolactin levels, improvements in depressive symptoms tend to parallel reductions in prolactin (Buckman and Kellner 1985); however, it should be noted that bromocriptine is a dopaminergic drug and can therefore exacerbate delusional/psychotic symptoms.

MEDICATIONS USED TO TREAT ENDOCRINE DISORDERS

The following drugs that are commonly used in the treatment of some endocrine disorders may be associated with depressive symptoms.

Corticosteroids

Use of corticosteroids may contribute to disorders of cortisol metabolism, triggering changes in mood, thinking, and behaviour. Risk factors include female gender (Rundell and Wise 1989), systemic lupus erythematosus, rapid changes in dose, and use of high doses. Depressive symptoms may occur early in the course of treatment or following

discontinuation of the medication (Lewis and Smith 1983). High doses of corticosteroids can also induce manic or delusional episodes that require intensive treatment.

Management of depression associated with corticosteroid treatment includes slowing the rate of dose increases and avoiding high doses when possible. A steroid regimen involving treatment on alternate days may be preferable to a daily dosing regimen (Cordess et al. 1981). TCAs may worsen steroid-induced psychosis, and their use should be avoided in patients on steroid therapy.

Anabolic Steroids

Both depressive and manic syndromes are associated with use of anabolic steroids. These drugs may be prescribed for myotonic dystrophy, hypogonadism, and related disorders; they are also commonly abused by weight lifters and other athletes. Recent estimates suggest that there may be more than 1 million users of anabolic steroids in the United States alone. Mood disturbance is seen in about 22% of individuals taking these drugs (Pope and Katz 1988) and occurs in a highly dose-dependent manner. Discontinuation may also cause depressed mood; however, depressive symptoms associated with withdrawal from anabolic steroids responds well to treatment with SSRIs (Malone and Dimeff 1992).

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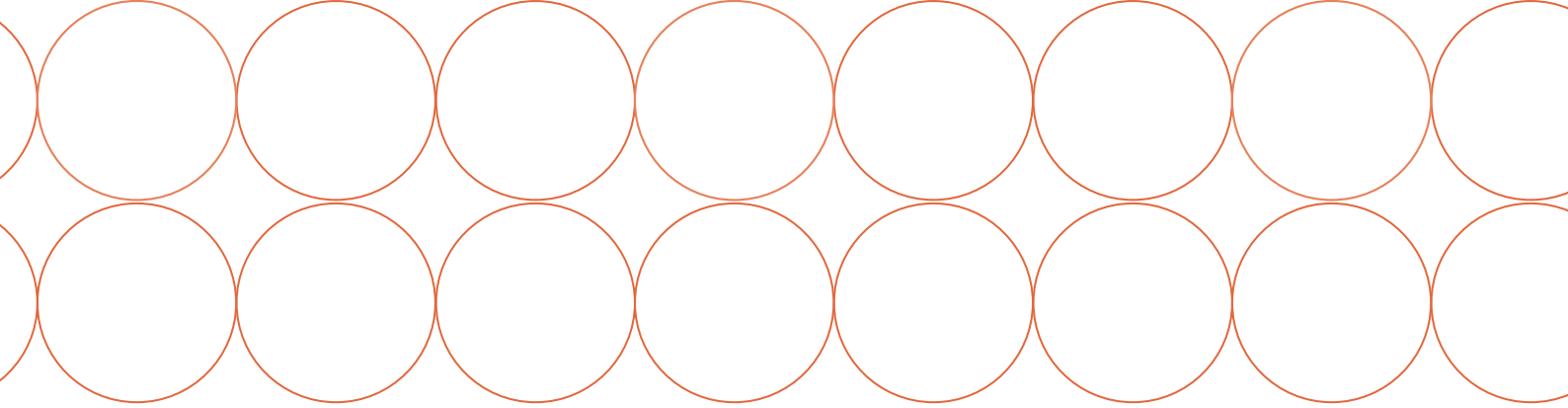

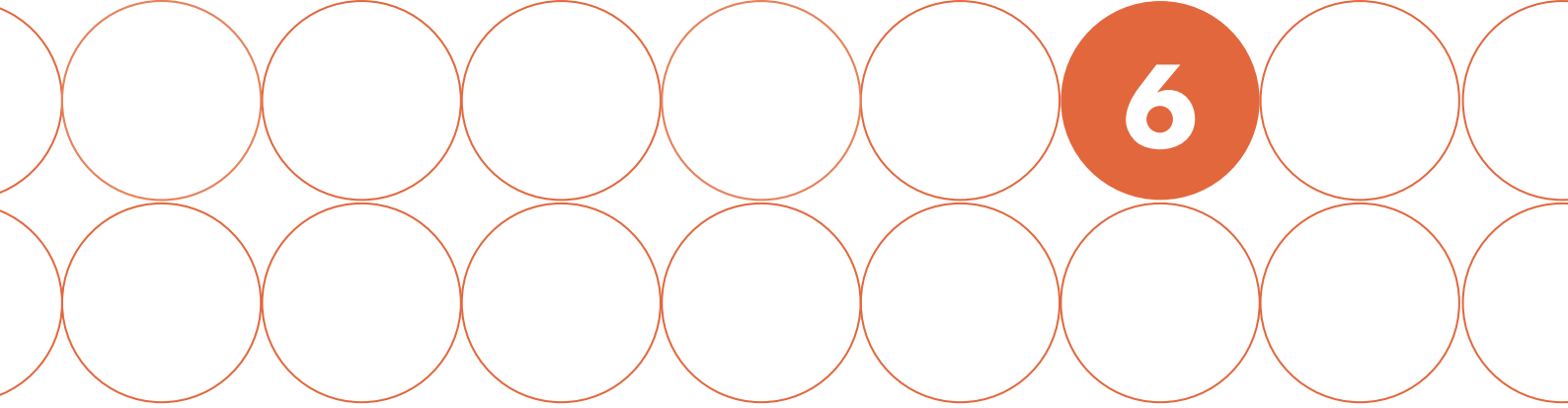

Chapter 6

Depressive Disorders in Oncology

Luigi Grassi, M.D. and Michelle Riba, M.D.

INTRODUCTION

Cancer is one of the most prevalent medical disorders throughout the world. It is estimated that the incidence of cancer will increase by 50% by the year 2020, with 16 million new cases in the year 2020. At the same time, earlier diagnoses and improvement in cancer therapies have allowed patients to survive with a better quality of life (WHO 2006).

Depression is among the most common and prevalent psychiatric disorders in cancer patients (Pirl 2004). Data accumulated over the last 20 years have investigated the epidemiology and pathogenesis of depressive disorders in patients with cancer, how depression influences patients' quality of life and the lives of their families, and the efficacy of psychiatric and psychosocial interventions in depressed patients with cancer (Chochinov 2001; Mermelstein and Lesko 1992; Rodin and Voshart 1986; Sellick and Crooks 1999). A 2007 Institute of Medicine Report noted that "Today, every individual treated for cancer can (and should expect to) have their psychological and social needs addressed alongside their physical needs."(Committee on Psychosocial Services to Cancer Patients/Families in a Community Setting et al. 2007).

It is generally recommended that increased attention be focused on the problem of depression in patients with cancer. In spite of the fact that cancer often precipitates the need for and use of mental health services (Hewitt and Rowland 2002), cancer patients with major psychiatric disorders, including depression, have been found to utilise mental health services at a low rate (Kadan-Lottick et al. 2005). Among cancer patients identified as having major depression, only half discuss their low mood with their general practitioner; only one-third receive any antidepressant medication; very few take a therapeutic dose for an adequate period; and very few receive psychological treatment or are referred for mental health services (Sharpe et al. 2004a). It is thus critically important for healthcare professionals in oncology, such as oncologists, surgeons and radiation oncologists, general practitioners, and nurses, to receive training and education in the area of psycho-oncology (Grassi et al. 2005a). Clinicians are referred to an online multilingual core-curriculum on "Psychosocial Aspects of Cancer Care" (Grassi and Uchitomi 2006), which can be accessed at http://www.ipos-society.org/professionals/meetings-ed/ed-online-lectures.htm.

PREVALENCE

As noted by Massie (2004), although many research groups have evaluated cancer patients for depression since the 1960s, the reported prevalence of depression (major depression, up to 38%; depression spectrum syndromes, up to 58%) has varied significantly because of the different concepts and criteria that have been used to define depression; the varying methodological approaches used to measure depression, and the nonhomonogeneous populations that were studied. In addition, the type and site of cancer, as well as the cancer stage, should be always considered in epidemiological studies of depression (Table 6.1) (Onitilo et al. 2006).

TABLE 6.1

Prevalance of depressive disorders by cancer site

Pancreas	33%-50%
Oropharynx	22%-57%
Breast	13%-46%
Lung	11%-44%
Colon	13%-25%
Gynecological	12%-23%
Lymphomas	8%-19%
Gastric	11%

Source: Massie 2004

Onset of depressive disorders can be triggered by several factors at different phases of the illness trajectory, such as the initial discovery of a suspicious symptom; hearing the diagnosis from a healthcare professional; awaiting treatment; during changes in treatment; at the end of treatment; when discharged from hospital; surviving cancer; failure of treatment; recurrence or progression of the disease; being at an advanced phase of illness; and approaching the end of life (Holland et al. 2006).

PATHOGENESIS

Several causes and risk factors for the development of depressive disorders in cancer patients have been identified, which tend to involve the interaction of psychological, social, and biological factors (Table 6.2) (Holland 1992). Psychological risk factors may include family history of depression; previous episodes of depression; and a tendency to consider stressful life events as uncontrollable (external locus of control). Poor support (e.g., from family and friends) and diffuse interpersonal ties (e.g., in neighbourhood and at work) represent possible social risk factors (Grassi et al. 1993, 1997). The most common biological factors associated with depression are the site of cancer and use of chemotherapeutic drugs (see below).

It has been shown that certain sites of cancer may influence depression. Pancreatic cancer has been indicated as a neoplastic disease that is frequently associated with depression (Boyd and Riba 2007). At the same time, studies tend to indicate that people with depression are at higher risk for developing pancreatic cancer (Carney et al. 2003). Thirty-five to 40% of patients with pancreatic cancer report depressive symptoms (Kelsen et al. 1995). Head and neck, lung, and gastrointestinal carcinomas are also associated with a higher risk of depression (Zabora et al. 2001).

TABLE 6.2

Risk factors for depressive disorders in individuals with cancer

Young age
Female gender
Receiving palliative treatment
Active symptoms of the disease
Advanced disease
Presence of uncontrolled pain
Moderate-to-severe disability or discomfort
Social isolation and poor social support
Recent losses
Socioeconomic pressures
Tendency toward pessimism and external locus of control
Alcoholism or substance abuse
History of mood disorders
Suicide attempts

Source: Holland 1992

Chemotherapeutic agents, such as methotrexate, vincristine, vinblastine, asparaginase, procarbazine, and interferon, have been reported to be associated with depressive symptoms (Adams et al. 1984; Middleboe et al. 1994). The role of pro-inflammatory cytokines such as interleukin-1 (IL-1), interleukin-6 (IL-6), and tumor necrosis factor alpha (TNF-alpha) have also been implicated in depression in patients with cancer (Raison and Miller 2003). Cancer patients with major depression have been reported to have markedly higher plasma levels of interleukin-6, more abnormal dexamethasone suppression tests, and higher cortisol concentrations than nondepressed patients (Soygur et al. 2007), with both IL-6 and variations in cortisol possible biological markers of depression in cancer patients (Jehn et al. 2006). Finally, certain brain structures, such as the amygdala, are believed to play a role in cancer patients with a history of depression (Yoshikawa et al. 2006).

DIAGNOSTIC CONSIDERATIONS

Many symptoms of depressive disorders are similar to those of cancer, including loss of appetite, loss of weight, insomnia, loss of interest and cognitive impairment, fatigue, and loss of energy. This makes the diagnosis of depression difficult in cancer patients. Some authors suggest including all of the symptoms in the assessment for depression, irrespective of the fact that these symptoms may be attributable to cancer (inclusive approach). It should be noted that certain symptoms (e.g., appetite-related symptoms and a diminished ability to think) seem to be useful in the diagnosis of depression, while others (e.g., sleep disturbances and fatigue) are not (Akechi et al. 2003). Other researchers have suggested the following approaches in assessing for depression in patients with cancer: replacing somatic symptoms with cognitive-affective items (substitute approach) (Endicott 1984); adding some new affective symptoms to the original criteria (alternative approach) (Von Ammon Cavanaugh 1995); or completely excluding somatic symptoms and using only affective symptoms to make the diagnosis (exclusive approach). An agreement on which method is the most specific has not been reached, although the exclusive approach has been reported to be the most valid and appropriate method of diagnosing major depression in cancer patients (Uchitomi et al. 2001). The following clinical vignette illustrates the difficulty of diagnosing depression in patients with cancer, the possible atypical presentation of depression in these patients, and the need for careful and comprehensive evaluation.

A number of simple screening instruments for depression have been proposed. The Distress Thermometer, which is rated on a scale of 0 to 10, was developed by the National Comprehensive Cancer Network (NCCN) (www.nccn.org) (Holland et al. 2007a and b) and has been proven to be helpful in detecting adjustment disorders and major depression in cancer patients by using cut-off scores for distress of "3/4" (Akizuki et al. 2005). A more conservative score of 5 seems to be useful in identifying patients with more moderate to severe depressive symptoms (Gil et al. 2005).

Chochinov et al. (1997) indicated that a single-item question "Have you been depressed most of the day, nearly everyday, for the past two weeks or more?" was able to identify all cancer patients diagnosed as depressed using the Research Diagnostic Criteria (RDC) (sensitivity 100% and specificity 100%). Other researchers have reported that this single question has lower ability to correctly detect depression among terminally ill cancer patients (Lloyd-Williams et al. 2003). In a Japanese study, the single-item question showed a sensitivity of 42% and a specificity of 86% (Kawase et al. 2006).

Clinical Vignette

Mary is a 53-year-old woman who underwent lumpectomy for breast cancer, followed by chemotherapy and radiotherapy, and then reconstructive surgery 2 years ago. She felt well until the last month when she started to complain of weakness, loss of appetite and weight, and a constant pain at the site of the operation and in the contralateral breast. In the last month, she has not been able to do her chores at home, instead spending most of her time in bed or sitting in a chair. Her general practitioner, who suspected a possible recurrence of cancer, sent Mary to the oncologist who ordered many different tests, including blood tests, CT scan, and PET, in order to assess for possible metastases. When all the tests were negative, a psychiatric consultation was requested. The patient had been living for 25 years with a man whom she felt was not supportive. In addition, her adult daughter and her husband had divorced 3 months earlier, and her daughter had subsequently been admitted to an inpatient psychiatry unit following a severe suicide attempt. In the meeting with the psychiatrist, Mary was not able to express her emotions in terms of sadness or low mood, but rather she reported a "feeling of not having feelings anymore". For Mary, time was "stuck", there was no future and she had a sense of emptiness. Her attention was focused on her pain and she had asked for a mastectomy of the contralateral breast because she was convinced that she had cancer, in spite of the negative test results. She also thought that there was something wrong in her reconstructed breast and that it would be better to have a mastectomy for that breast as well. She expressed the thought that, if the pain continued, life was not worth living anymore. Mary reported that she felt worse in the morning and a little better in the evening, while night was a relief, since it was the only time of the day when she did not think about pain. The pain seemed to leave her in peace only at night, while she described the morning as "just the beginning of a new nightmare". A diagnosis of major depression was made and treatment was initiated with an antidepressant in combination with interpersonal psychotherapy. After 4 weeks of treatment, the situation was still not completely solved and the antidepressant dose was increased, which was followed by remission of symptoms in 3 weeks.

CONSEQUENCES OF DEPRESSION IN CANCER PATIENTS

Assessment and treatment of depression among cancer patients is important. Several studies have indicated that depression is associated with maladaptive coping and abnormal illness behaviour, such as a tendency to react excessively in interpersonal relationships (irritability); to adopt a pessimistic attitude about the illness (hopelessness); and to focus attention on physical symptoms interpreting them as a sign of illness (anxious preoccupation) (Grassi et al. 1993; Grassi and Rosti 1996). Depression has been shown to have a negative influence on several dimensions of the patient's quality of life (Parker et al. 2003). As discussed in more detail in the following sections as well as in Volume II, Chapter 9 "Depressive Disorders and Pain", depression affects the patient's perception of pain as well as suicide ideation. Researchers have also examined biological effects associated with the relationship between depression and cancer. Depressed patients with breast cancer, for example, seem to have less response to chemotherapy agents (Walker et al. 1999), and some data has indicated a possible, yet not fully understood role, of depression in increasing the risk of recurrence and in reducing survival among breast cancer patients (Hjerl et al. 2003; Watson et al. 1999, 2005). It is possible that effects on adherence to treatment, maintenance of high-risk behaviour, and an hypothesised direct link between immunity and cancer (Reiche et al. 2005; Spiegel and Giese-Davis 2003) explain this relationship, although caution is needed in interpreting the data that are emerging in this area. Finally, depression reverberates within the family, so that both emotional distress and the rate of psychiatric diagnoses (e.g., major depression, general anxiety disorders) are higher among caregivers of cancer patients than in the general population (Couper et al. 2006; Heaven and Maguire 2003). In the case of the patient's death, the risk of complicated or traumatic grief is higher in families that showed psychosocial disorders and maladaptive coping before the loss (Kissane et al. 1997, 2003).

SPECIAL PROBLEMS

Cancer Pain

Pain is one of the most common symptoms reported by cancer patients. Cancer pain, especially when under-evaluated and thus under-treated, is accompanied by profound suffering, fear of death without dignity, hopelessness, and helplessness. Pain and depression are closely linked, so that uncontrolled pain is associated with a higher risk of developing depression, while depressed patients report a higher perception of pain (Valentine 2003). Studies have reported that almost half of cancer patients who received a psychiatric diagnosis experienced significant pain (Derogatis et al. 1983). Pain also appears to precipitate major depression in cancer patients without a family or personal history of depression (Spiegel et al. 1994). Pain is also associated with a desire for hastened death (see below) (O'Mahony et al. 2005). Acute pain is often associated with treatment, while chronic cancer pain tends to be associated with the state of the disease. The mental state of patients with cancer should be assessed frequently in order to identify the presence of depression or other psychiatric disorders.

Suicide

Suicidal ideation is a serious and worrisome concern. Although suicide has been reported to be 1.5–2 times higher in cancer patients than in the general population (Hem et al. 2004), the risk is increased by a number of factors, of which depression is one of the most important (Table 6.3). The risk of suicide is closely related to the request for a hastened death and assisted-suicide. Among terminally ill patients with cancer, the request for euthanasia is about 4 times higher in patients with depression than those without depression (Van der Lee et al. 2005). Depression and hopelessness are independent and unique predictors of desire for a hastened death among terminally ill cancer patients (Breitbart et al. 2000). Limited social support, poor physical conditions, and low spirituality are other factors that are also associated with a desire for death (McClain et al. 2003; Wilson et al., 2007). Treatment of patients with cancer should include interventions aimed at early recognition of depression as well as regular assessment for risk factors for suicide.

TABLE 6.3

Predicators of suicide risk in patients with cancer

Medical	Poorly controlled pain, advanced stage of disease with a poor prognosis, disinhibition due to delirium, physical impairment and other severe physical symptoms, fatigue
Personal	Family history of suicide, prior psychiatric disorder, prior depressive disorders or suicidal attempts, substance/alcohol abuse, depressive symptoms and hopelessness, loss of control (helplessness and inability to control one's environment), recent bereavement, and few social supports

CLINICAL FEATURES/ SYMPTOMATOLOGY

A patient with cancer who has a depressive disorder is likely to present with depressive symptoms characterised by preoccupation with the illness and feelings of hopelessness for the future. The patient goes through phases, similar to the grieving response, in response to the diagnosis. From the nosological point of view, adjustment disorders with depressive symptoms are commonly seen in cancer patients (such symptoms have been reported in up to 68% of patients). Symptoms include depressed mood, anxiety, and mixed emotional disturbances.

Well-defined, major depressive disorders may be triggered by the disease itself, by chemotherapeutic agents, or as a functional response to cancer-related disabilities. Feelings of worthlessness and guilt have been found to be powerful discriminating factors between the "normal" sadness seen in cancer and a major depressive disorder. Recurrent thoughts of suicide are common in cancer patients, but the intensity of the desire can help differentiate a major depressive disorder from a normal reaction. In the oncology setting, mood disorders or symptomatic depressive disorders can be the result of treatment with steroids. Steroids can cause a depressive syndrome that is indistinguishable from a functional mood disorder, both in presentation and in its response to antidepressant medications.

Sub-threshold depressive disorders or mixed anxiety and depressive disorders may also occur, and can pose problems in the differential diagnosis with other affective dimensions related to cancer.

Demoralisation is considered a specific clinical condition that should be separated from adjustment disorder and major depression and which merits consideration in the spectrum of mood disorders that may occur in medically ill patients (Clarke et al. 2005; Grassi et al. 2007; Mangelli et al. 2005). According to some authors (Kissane et al. 2001), the core symptoms of a demoralisation syndrome in medically ill patients, including patients with cancer, are:

1. affective symptoms of existential distress including hopelessness or loss of meaning and purpose in life;
2. cognitive attitudes of pessimism, helplessness, a sense of being trapped, personal failure, or lacking a worthwhile future;
3. absence of drive or motivation to cope differently;
4. associated features of social alienation or isolation and lack of support;
5. allowing for fluctuation in emotional intensity, these phenomena persist for more than 2 weeks;
6. a major depressive episode or other psychiatric disorder is not present as the primary condition.

In oncology, demoralisation has been shown to occur in at least 20% of patients who did not meet the criteria for any DSM-IV diagnosis (Grassi et al. 2005b), indicating the need for more attention to the psychosocial concomitants of cancer.

MANAGEMENT CONSIDERATIONS

Other chapters in this program provide recommendations for the general management of depression and information on the consequences of potential drug-drug interactions in the treatment of depressive disorders in the medically ill. However, a number of specific issues should be kept in mind in assessing and treating depression in patients with cancer. Clinicians should exercise special care when communicating and relating to cancer patients. Over the last 10 years, training courses and educational material on this subject have been developed and evaluated in randomised clinical trials with promising results (Fallowfield and Jenkins 2006; Jenkins et al. 2005). Some guidelines, such as the SPIKES protocol (Table 6.4) (Baile et al. 2000), help physicians with the process of communicating the diagnosis of a life-threatening condition, such as cancer. Paying attention to the patient's interpersonal situation and assessing his or her psychological status and capacity to sustain receipt of the information are necessary steps in communicating in this situation. If a patient is thought to be psychologically vulnerable, appropriate support should be offered immediately, along with regular medical follow-up.

It is useful to explain the pathogenesis of the disease, if known, in clear, simple terms without overloading the patient with medical jargon and confusing scientific information. It is also important to extend support for the entire duration of the illness—not just during the acute phase—to assess the evolution of the patient's psychological status (coping mechanisms, distress, elicited social support) and to maintain a trustful relationship and hope. The clinician should take a respectful and positive attitude, treating the patient as a person rather than as the survivor of a serious and sometimes fatal disease. Patients tend to adhere better if they believe they can contribute toward their recovery. Suggesting the use of techniques such as relaxation, yoga, visualisation, exercise, or a healthful diet can help. Patients should also be encouraged to be open about their diagnosis with close friends and relatives. Secretiveness contributes to poor psychological adaptation.

Physicians should be aware that, in the end-stages of a chronic, life-threatening disease such as cancer, patients may be tempted to request that the doctor assist them in suicide, or they may commit suicide, because of poorly controlled pain, a serious deterioration of their physiological condition, and/or loss of dignity, especially if a concomitant severe depressive episode is present (see earlier

TABLE 6.4

The six-step protocol for communication in cancer (SPIKES)

STEP 1: S	SETTING UP the Interview
STEP 2: P	ASSESSING THE PATIENT'S PERCEPTION (of his/her situation)
STEP 3: I	OBTAINING THE PATIENT'S INVITATION (to receive information)
STEP 4: K	GIVING KNOWLEDGE AND INFORMATION TO THE PATIENT
STEP 5: E	ADDRESSING THE PATIENT'S EMOTIONS WITH EMPATHIC RESPONSES
STEP 6: S	STRATEGY AND SUMMARY

Source: Baile et al. 2000

discussion of suicide). Such a request presents a major ethical challenge, and a precipitous response is inappropriate, since the "free choice" of patients can fluctuate, depending on their psychological status, sense of hope, and pain level at the moment. Support often can and should be more directive, since effective management of the depressive disorder with appropriate treatment may motivate a patient to "collaborate" better in coping with the disease. Physicians report difficulties in assessing and managing depression in patients receiving palliative care. Such difficulties occur especially in distinguishing symptoms of depression from sadness and in deciding what treatment for depression is appropriate when the patient's life expectancy is short (Lawrie et al. 2004). In this situation, close co-operation with psychiatric/psychological teams is essential.

INTERVENTIONS

Interventions in cancer patients with depression consist of psychopharmacological and psychosocial treatment. Given the clinical importance of this area, several recent meta-analyses have examined the efficacy of such interventions and addressed the need for more specific guidelines for treatment of depression in patients with cancer (Newell et al. 2002; Rodin et al. 2007; Williams and Dale 2006).

Psychopharmacology

Psychopharmacology in oncology has changed extensively over the past 10 years (Schwartz et al. 2002). Older antidepressants, such as the tricyclic antidepressants (TCAs), are used less often than in the past because their side-effect profile (e.g., dry mouth, constipation, sedation, and confusion) is especially problematic for cancer patients. A large body of experience has been accumulated on the use of newer antidepressants in oncology patients (Kim and Fisch 2006). Data have been published concerning the use of selective serotonin reuptake inhibitors (SSRIs), such as fluoxetine, citalopram, paroxetine, and sertraline (Fisch et al. 2003; Holland et al. 1999; Pae et al. 2004; Theobald et al. 2003; Torta et al. 2008), norepinephrine reuptake inhibitors such as reboxetine (Grassi et al. 2004), and benzamides such as amisulpride (Torta et al. 2007). The advantages and disadvantages of specific agents should be balanced in an individualised way that takes into account the patient's physical condition, the type of depression (agitated/slow), and the side-effect profile of the agent being considered. Thus, clinicians can match the side-effect profile of the agent to the patient on a case-by-case basis and, when appropriate, may be able to take advantage of side effects that would be beneficial in particular situations (e.g., increase of appetite caused by the drug mirtazapine in patients with poor appetite; increased intestinal motility associated with some SSRIs in patients taking opioids). When tolerated, TCAs, given in lower doses and for shorter intervals, can be useful in treating both depressive symptoms and pain (Chaturvedi et al. 1995). Duloxetine, with its dual effects on mood and pain, represents a new and interesting possibility for treating depression in cancer patients.

Psychostimulants, such as dextroamphetamine, methylphenidate, and pemoline, used in low doses have been considered for treating depressive symptoms in terminally ill patients because of their rapid onset of action and positive effects on attention, concentration, psychomotor activity, appetite, weakness and fatigue, and opioid-induced sedation (Homsi et al. 2000). Recently, modafinil, a drug with memory-improving and mood-brightening effects, has been used to counterbalance fatigue in cancer patients (Carroll et al. 2007) and to treat depression; this agent is a possible alternative to classic psychostimulants because of its low potential abuse and its relatively safer side-effect profile (Konuk et al. 2006; Orr and Taylor 2007).

Several studies have also reported the efficacy of antidepressants, such as venlafaxine, mirtazapine, and paroxetine, as adjunctive agents for the treatment of hot-flashes (De Sloover Koch and Ernts, 2004) and pruritus (Greaves 2005) in cancer patients, independent of their effects on mood.

Drug Interactions Relevant to Cancer Patients

Both TCAs and newer antidepressants, such as fluoxetine and venlafaxine, potentiate the analgesic effects of morphine. Caution is needed when prescribing SSRIs to patients who are receiving tramadol, because of its serotonergic action and the risk of a serotonergic syndrome. Desipramine inhibits the metabolism of morphine and methadone and may increase plasma levels of these opioids. Methadone may inhibit the metabolism of desipramine. Propoxyphene can inhibit metabolism of doxepin and other TCAs, resulting in an elevation of serum levels. Antidepressants with anticholinergic side effects may aggravate certain symptoms, such as constipation, dryness of mouth, and confusion related to chemotherapy, narcotics, or the advanced phase of illness.

Serious drug interactions may occur between antidepressants and certain chemotherapeutic agents. Fluoxetine can interact with procarbazine, an antineoplastic drug that inhibits monoamine oxidase (MAO), and the combination of these two agents can result in an MAOI/fluoxetine-like interaction. When a patient has been treated with fluoxetine, a 5-week washout period is needed before starting procarbazine. Cisplatin and lithium carbonate, when given together, can increase risk of renal toxicity. Recent reports indicate that some antidepressants may affect the metabolism of tamoxifen, a selective estrogen receptor modulator used in the long-term treatment of patients with breast cancer. Certain antidepressants, especially paroxetine, have an inhibitory effect on the cytochrome P450 CYP2D6 system and can thus reduce levels of endoxifen, the active metabolite of tamoxifen, by 38%–58% and consequently reduce the effect of the treatment in patients with breast cancer (Jin et al. 2005).

Psychosocial Treatment

The literature on psychosocial treatment in cancer has increased, with data indicating the need to adapting psychotherapy for the specific context of oncology (Bloch and Kissane 2000) and to create new approaches for dealing with the specific issues raised by cancer. Significant steps have been made in psychosocial interventions for the advanced phases of cancer, in which there is a great need to help patients maintain their dignity and to enhance the spiritual aspects of dying (Breitbart 2002; Chochinov et al. 2005).

Several studies have shown that psychological interventions can produce significant improvement in patients' quality of life and can reduce emotional symptoms, including depression, and maladaptive coping styles (e.g., hopelessness and anxious preoccupation) (Sheard and Maguire 1999). Accurate diagnosis and referral for appropriate psychological intervention are necessary to increase the likelihood of benefit and reduce drop-out rates among depressed patients with cancer. Psychotherapy (both individual and group format) has shown the most effective results in cancer patients with well-defined depressive symptoms, while psychotherapy interventions in patients with "normal" psychological distress have shown few or no effects (Coyne et al., 2006; Fawzy et al. 1995). Preliminary data suggesting that psychosocial interventions might increase duration of survival in cancer patients (Spiegel et al.1989) have not been confirmed by more recent studies (Goodwin et al. 2001; Kissane et al. 2007; Spiegel et al. 2007) which did not find that psychotherapy improved patients' cancer prognosis.

As a general recommendation, the combination of psychological interventions and pharmacotherapy tailored to the specific patient's needs should be considered as the best choice for treating depression in cancer settings. Positive effects in reducing psychiatric disorders, especially depression, have been reported by several authors when guidelines for screening, proper diagnosis, and psychological and psychopharmacological approaches are available to clinicians (Akechi et al. 2007; Sharpe et al. 2004b). Similar findings have been reported concerning the use of the recently developed NCCN guidelines for supportive care-distress management in mood disorders (Holland and Bultz 2007; NCCN 2008).

CONCLUSIONS

Depression is an important comorbid psychiatric disorder in patients with cancer. The recent report from the Institute of Medicine of the National Academies, "Cancer Care for the Whole Patient: Meeting Psychosocial Health Needs", is an important roadmap for addressing the depression and anxiety that frequently develops in patients with cancer (Committee on Psychosocial Services to Cancer Patients/Families in a Community Setting et al. 2007). This Institute of Medicine report provides a blueprint for what should be standard psychosocial care for patients with cancer. It is important for psychiatrists to work with their medical colleagues to develop best practices to be used in screening for and detection of depression and other psychiatric problems in patients being treated in the oncology setting. In addition, evidence-based clinical trials are needed to determine which are the best treatments for depression for patients at all stages of disease and in all types of cancer. As new technologies are developed and more powerful chemotherapeutic and non-chemotherapeutic agents for the treatment of cancer are brought to clinical trials, we need to continue to enlarge our understanding of the impact of these treatments on the psychiatric care of patients and their families.

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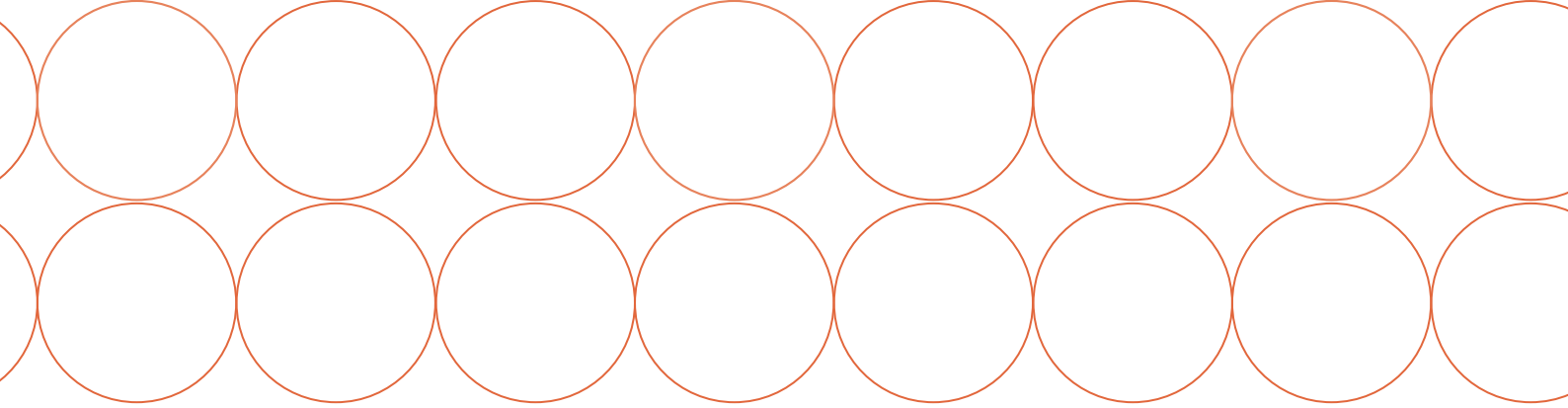

Chapter 7

Depressive Disorders in other Selected Medical Conditions

Patients with medical illnesses other than those described in the other chapters in this Volume may present with depressive disorders or depressive symptoms during the course of their illnesses. Because it is not possible to deal with all medical conditions in this volume, conditions that are frequently associated with depressive disorders and that may serve as paradigms for related illnesses have been selected for discussion. For example, the section on rheumatoid arthritis has relevance for the management of depressive disorders in patients with diseases of the musculoskeletal system.

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RHEUMATOID ARTHRITIS

The prevalence of depressive disorders in rheumatoid arthritis (RA) is similar to that seen in other chronic medical diseases. Factors such as severity of physical illness, disability, level of social support, and previous psychological state are also relevant to the development of depressive disorders in these patients. Other predictors of depression are high tension, low self-esteem, perceived impact of the RA, fatigue, passive coping, medication effectiveness, and pain (Covic et al. 2006). Both physical and psychological factors have an impact on depression in RA. A systematic review has noted that depression is more common in patients with RA than in healthy individuals. This difference is not due to sociodemographic factors, but it may be attributable, in part, to the levels of pain experienced (Dickens et al. 2002). The diagnosis may be complicated by the presence of symptoms that are common to both RA and depressive disorders (Table 7.1).

Assessments of pain and mood in RA reveal two patterns. In the first pattern, mood changes either precede or accompany changes in joint pain and tenderness; patients with this pattern have a good prognosis. In the second pattern, pain is inversely related to the intensity of mood disturbance; patients with this paradoxical pattern tend to have a poor prognosis. Perceived lack of control over pain is another important predictor of mood disturbance in RA (Covic et al. 2006).

Patients with RA with a history of two or more episodes of major depression have been reported to have more pain at baseline, and exhibit higher levels of pain in response to stress induction than patients with RA who have had only one depressive episode or have no history of depression (Zautra et al. 2007). The intensity of pain may be related to the RA rather than to depression or mood changes. Other factors that mood in RA are the patient's reaction to the diagnosis, coping style, feelings of helplessness, and availability or lack of social support.

Management of depression in patients with RA generally involves the use of antidepressants, because they not only relieve depressive symptoms but may also may alleviate pain and decrease antibody titers. Selective serotonin reuptake inhibitors (SSRIs) and serotonin norepinephrine reuptake inhibitors (SNRIs) seem to be safe and effective; Tricyclic antidepressants (TCAs) may increase the risk of orthostatic hypotension, which could be hazardous for patients with RA. Benzodiazepines may be useful in treating associated insomnia, muscle spasm, and anxiety. In addition, cognitive-behavioural psychotherapy may be a useful adjunct.

Clinicians should be aware that TCA and tetracyclic plasma concentrations may be increased if acetylsalicylic acid (aspirin) is used as an anti-inflammatory analgesic. Because absorption of non-steroidal anti-inflammatory drugs (NSAIDs) may be delayed in patients taking TCAs or antidepressants with anticholinergic side effects, dose adjustments may be required.

Patients should educated that the goal of treatment for RA is management, not cure. If cultural considerations cause the patient to self-blame, he or she should be helped to understand that the disease is not a "punishment" for past deeds or karma.

TABLE 7.1

Symptoms shared by rheumatoid arthritis and depressive disorders

Feeling helpless and hopeless
Inability to work
Insomnia
Lack of energy
General poor health

PEPTIC ULCER

For many years peptic ulcer was regarded as a classic "psychosomatic disease"; however, it now generally considered a physical illness since Helicobacter pylori (H. pylori) was identified as the primary etiological factor involved. The prevalence of anxiety and depression in peptic ulcer may not be increased (Lewin and Lewis 1995), but recent evidence suggests a specific link with anxiety disorders and neuroticism (Goodwin and Stein 2002, 2003), which has not to date been explained. Additional suggestions that there may be a link with psychological factors are the association that has been reported between onset of peptic ulcer disease and "goal-frustrating" life events (Craig 1989; Ellard et al. 1990), as well as reports of the development of peptic ulcer disease after the experience of an earthquake, a situation in which stress and the presence of H. pylori interacted (Matsushima et al. 1999). Recent evidence suggests that smoking, use of non-steroidal anti-inflammatory drugs, and psychological stress (or use of minor tranquillisers) appear to be independent risk factors for development of peptic ulcers (Anda et al. 1992; Levenstein et al. 1997; Rosenstock et al. 2003). Depressive disorders that occur concurrently with peptic ulcers should be treated because they are associated with impaired health-related quality of life (Dimenas et al. 1995), and depression also adversely affects the outcome of standard treatment for peptic ulcer (Xuan et al. 1999).

FUNCTIONAL BOWEL DISEASE

Functional bowel disorders are responsible for approximately 40% of new gastroenterology outpatients and numerous consultations in primary care. The most common disorders in this group of conditions include irritable bowel syndrome and functional dyspepsia. These disorder are associated with impaired health-related quality of life, work absenteeism, and depressive and anxiety disorders (Creed et al. 2006; Drossman et al. 2002; Henningsen et al. 2003;Whitehead et al. 2002).

The Relationship Between Functional Bowel Disease and Psychiatric Disorders

The prevalence of depressive and anxiety disorders in clinic patients with functional bowel disorders is so high (Whitehead et al. 2002) that these disorders have been considered to be a form of psychiatric disorders; however, this is not so (Creed et al. 2006). There is a close relationship between stress and gut function. Diarrhoea and constipation are among the core symptoms of anxiety and depressive disorders and there is an overlap in the risk factors for functional bowel disorders and depressive disorders (e.g., both are more common in women than men).

On the other hand, population surveys show less overlap between functional bowel disorders and depressive disorders than clinic studies, suggesting that treatment seeking may be associated with depression (Boyce et al. 2006); yet over half of clinic patients do not have depressive disorder. In addition, gastroenterologists now recognise "extra-intestinal" symptoms of irritable bowel syndrome (e.g., headache, backache); however, these symptoms occur only in a minority of patients with irritable bowel syndrome and probably represent an overlap with somatisation (defined as a high number of bodily symptoms) (Creed et al. 2006). One study found that 49% of patients with functional bowel disorders had a psychiatric disorder: in 24% of these patients, the psychiatric disorder occurred first, while in the other 25% of patients, the onset of the psychiatric disorder coincided with onset of the functional bowel disorder (Craig et al. 1989).

Functional bowel disorders and depressive/anxiety disorders are best regarded as separate conditions that often occur together. It is important to identify depressive disorders and somatisation in patients with functional bowel disorder because these disorders are associated with impairment of health-related quality of life and high healthcare costs in these patients (Creed et al. 2005a; Spiegel et al. 2005).

Precipitating life events

Two thirds of patients with irritable bowel syndrome have experienced a severe social stress, such as bereavement, marital separation, or other interpersonal difficulties just prior to onset of the abdominal symptoms. The pattern of social stress before onset of functional abdominal pain is strikingly similar to that preceding depressive disorders and before self-harm (Creed et al. 1988).

Childhood antecedents including abuse

There is evidence that childhood abdominal pain may precede functional bowel disorders in adult life; environmental factors may be more important than genetic influences in this relationship (Levy et al. 2001). Recurrent abdominal pain in children is associated with mothers who have a high neuroticism score and with the development of numerous bodily symptoms later in life (Hotopf et al. 1998, 1999). There is a clearly documented association between irritable bowel syndrome and a history of abuse. The latter is known to be associated with somatisation, which appears to mediate the association between irritable bowel syndrome and abuse and its adverse effect on outcome (Creed et al. 2005b; Fiddler et al. 2004; Salmon et al. 2003).

Associated features

Gastroenterologists may encounter difficulties in managing the treatment of some patients with functional bowel disorders. Such cases usually involve patients who have high anxiety about their health, catastrophising cognitions (e.g., "this pain is terrible—I cannot go on living like this"), or specific anxiety about gastrointestinal problems such as fears about cancer or losing control of one's bowels. All of these problems are worsened by comorbid anxiety, depression, and/or somatisation, so that it is important that gastroenterologists be advised to screen for these psychiatric disorders (Levy et al. 2006).

Management

A crucial component in the good management of functional bowel disorder is a satisfactory doctor-patient relationship, which will help the doctor understand the patient's fears and offer a full explanation of the symptoms using a biopsychosocial model (Creed et al. 2006; Spiller et al. 2007). The doctor should assess for depressive, anxiety, and somatisation symptoms in a clinical interview or by using a screening questionnaire (Creed et al. 2006). There is good evidence that TCAs can relieve some of these symptoms as long as the patient adheres to treatment (Drossman et al. 2003). The SSRI antidepressants may also be helpful for patients with irritable bowel syndrome, although their mode of action is not clear (Creed 2006; Creed et al. 2003). Treatment with an SSRI is a cost effective way of improving health-related quality of life without affecting severity of abdominal pain; the effect is due to reduction of depression (Creed et al. 2003). Cognitive-behaviour therapy and psychodynamic interpersonal therapy are also effective treatments for these patients (Guthrie et al. 1991; Kennedy et al. 2005; Lackner 2004). None of these antidepressant or psychological therapies seem to work primarily by treating depression; however, when the depression is also successfully treated, the effect on the bowel symptoms and health-related quality of life is marked. Psychiatrists should be prepared to work closely with gastroenterologists and primary care doctors in the management of these patients. Gastroenterologists and primary care doctors should also be encouraged to assess for and treat depressive and anxiety disorders in their patients and to refer patients who have severe depression, suicidal ideas, a history of abuse, or personality difficulties associated with persistent functional bowel disorders to psychiatrists or psychologists for specialised assessment and care.

HEPATIC DISORDERS

Neuropsychiatric symptoms in liver disease range from depression to hepatic encephalopathy. The fixed facial expressions, psychomotor retardation, and mood swings characteristic of hepatic disorder may lead to an erroneous diagnosis of a depressive disorder (Lishman 1998). These neuropsychiatric symptoms are largely due to cerebral intoxication by nitrogenous intestinal contents not metabolised by the liver. Symptoms fluctuate and improve with treatment of the liver disease. Depression in patients with hepatitis C has been reported to be associated with poorer work and social adjustment, less acceptance of the illness, greater illness stigma, reduced ability to think and concentrate, and higher levels of subjective physical symptoms (Golden et al. 2005). Given the high prevalence of depression and the widespread use of antidepressants, physicians should keep in mind the possibility that these medications can cause hepatitis and consider early discontinuation of an antidepressant if the condition is suspected (Carvajal Garcia-Pando et al. 2002). Most antidepressant agents have the potential to produce idiopathic liver injury. There is no way to prevent idiopathic drug-induced liver injury, but the severity of the reaction may be minimised with prompt recognition and early withdrawal of the agent. The clinician must be careful to provide ongoing therapy of the underlying depressive disorder and be aware of possible drug discontinuation syndromes should potential hepatotoxicity be suspected (DeSanty and Amabile 2007).

Patients with hepatitis C have increased rates of major depression (as well as substance abuse). Treatment of hepatitis with interferon provokes episodes of depression in as many as a third of patients (Angelino and Treisman 2005). Depression has also been reported in about 17% of patients who have undergone orthotopic liver transplantation with higher rates in those who received liver transplants due to hepatitis C (Tombazzi et al. 2006).

Case Example

A 45-year-old widow was being treated for long-standing alcohol dependence, when underlying depressive symptoms emerged. Her liver functions were moderately abnormal, making the choice of antidepressant difficult. As discussed above, in selecting treatments for such a patient, clinicians should keep in mind that:

- Most antidepressants undergo extensive hepatic oxidative metabolism and should be dosed cautiously (Robinson and Owen 2005).
- Antidepressants can cause hepatitis (Carvajal Garcia-Pando et al. 2002).
- Most antidepressant agents have the potential to produce idiopathic liver injury.
- Early discontinuation of an antidepressant should be considered if hepatotoxicity is suspected.
- Possible drug discontinuation syndromes can occur if antidepressants are stopped due to hepatotoxicity.
- Idiopathic drug-induced liver injury cannot be prevented, but the severity of the reaction may be minimised with prompt recognition and early withdrawal of the agent.
- Ongoing therapy of the underlying depressive disorder should be provided using psychological or safe pharmacological methods.

RENAL DISORDERS

Depression is the most frequent psychiatric problem in patients with chronic renal disease and may have an effect on treatment outcomes and mortality (Fabrazo and De Santo 2006). Depressive symptoms are common in end-stage renal disease (uremia) and are sometimes the first manifestations leading to psychiatric consultation (Lishman 1998). Symptoms are similar to those of neurasthenia and may include lethargy, anorexia, and depression. Cognitive impairment occurs over time and fluctuates in association with depressive symptoms. In a systematic review on end-stage renal disease, the weighted mean prevalence of depression was reported to be 27% (with a range of 5% to 58%) (Murtagh et al. 2007).

The aetiology of these symptoms is related to metabolic changes, which may include accumulation of sedatives and other drug-induced metabolic disturbances, and to the psychosocial aspects of chronic renal failure, such as restrictions imposed by the need for lifelong dialysis. Depressive symptoms have also been attributed to electrolyte disturbances involving sodium, potassium, calcium, chloride, phosphate, and acid-base balance. Blood urea can serve as an indicator of the severity of overall metabolic disturbance. Symptoms generally improve with dialysis. Depression in chronic renal disease is linked to stressful life events and dependence, which could lead to suicide (Fabrazo and De Santo 2006). As observed with other comorbid illnesses, depressive disorder worsens the outcome for patients with kidney disease by increasing both morbidity and mortality.

One study found that depression was not associated with mortality in patients with kidney disease when gender, age, and treatment modality were controlled for. Transplantation was the main factor associated with lower mortality rates. However, depression was a strong predictor of quality of life, with the number of depressive symptoms directly associated with lower quality of life (Zimmerman et al. 2006). Treatment of depressive symptoms in patients with renal failure increases acceptance of medication treatment and therefore has the potential to improve overall patient outcomes. Concerns about the safety of antidepressant treatment in subjects with renal failure are often counterbalanced by the risks associated with comorbid depression, provided that antidepressants with a low volume of distribution and low protein binding are prescribed, and most importantly, that low initial doses are used. It is also recommended that, before starting an antidepressant treatment, clinicians research whether the agent being considered is liable for interactions related to the cytochrome P450 (CYP) isoenzyme system (Tossani et al. 2005). There is evidence that SSRIs may help control hypotension during dialysis (Yalcin et al. 2002). Clinicians should also be aware of the potential for interactions between immunosuppressant medications and antidepressants in patients who have undergone renal transplantation (Robinson and Levenson 2001).

CHRONIC PAIN

A more detailed discussion of pain and depressive disorders is provided in Volume II, Chapter 9. However, it is relevant to review some key points here. Pain is among the most frequent presentations in primary health care. Long-lasting pain is associated with depressive disorders, and a depressive disorder may also express itself in terms of pain. The neurobiology of pain and depression overlap (Clark and Chodyncki 2005). A recent literature review of data concerning the prevalence of depression and pain found that the prevalence of pain in depressed cohorts and the prevalence of depression in pain cohorts were higher than when these conditions were examined individually. The presence of pain has a negative effects on the recognition and treatment of depression. When pain is moderate to severe, it impairs functioning and may also be refractory to treatment. Such pain is associated with greater depressive symptoms and worse depression outcomes, as manifest in lower quality of life, decreased work functioning, and increased use of health care resources (Baer et al. 2003). Patients with chronic pain are frequently convinced that their pain is organic in origin, deny any psychological problems, and may be reluctant to consider nonsomatic causes or treatment.

Depression in patients with pain is associated with more pain complaints and greater impairment (Baer et al. 2003). Self-reported depressive symptoms are related to the evaluative or cognitive components of pain (Clark and Chodyncki 2005). There is a complex and intricate relationship between chronic pain, somatisation, illness behaviour, and depression. Appropriate investigations should be conducted to identify the physical causes of pain, as well as its nature, severity, frequency, and duration. Visual analogue scales have been widely used to measure intensity of pain, change in pain intensity, distress due to pain. and response to treatment (Chaturvedi et al. 2006).

Treatment

Antidepressants, especially TCAs, can be used effectively in this population and are often effective in reducing pain, restoring normal sleep, diminishing dysphoria, anxiety, and fatigue, and enabling the patient to engage more energetically in rehabilitation. The neurobiology of pain suggests that all antidepressants may potentially be efficacious for the treatment of chronic pain (Lynch 2001). Antidepressants may produce antinociceptive effects through a variety of pharmacological mechanisms (Ansari 2000). Clinical trials have found the efficacy of SSRIs in chronic pain syndromes to be variable and inconsistent (Clark and Chodyncki 2005). Duloxetine has been found to be effective in the treatment of major depression and pain complaints (Detke et al. 2002). When a patient with chronic pain shows a good global response to pharmacological treatment in both pain and depressive symptoms, this suggests that the patient may have an underlying depressive disorder.

TCA and tetracyclic plasma concentrations may be increased by acetylsalicylic acid (aspirin) used as an anti-inflammatory analgesic for pain. Conversely, absorption of NSAIDs may be delayed in patients taking TCAs or antidepressants with anticholinergic side effects, so that doses of NSAIDs may need to be adjusted. Counselling and cognitive and supportive therapy may also be used in patients with chronic pain; however, dynamic and psychoanalytic psychotherapies are generally not recommended. If various approaches are not successful in alleviating pain, it may be necessary to help the patient learn how to cope better with the pain.

Clinical Vignette

A 35-year-old woman reports that she has been having backache, headache, and pain in her limbs and neck for the past 2 years. She has also been diagnosed with depressive disorder and has been receiving irregular treatment for her depressive symptoms for the past year. She remains dissatisfied with her current status due to persistent aches and pain in her body, low mood and disinterest, and poor sleep.

In deciding on a treatment plan for such a patient, the clinician should consider the following issues:

Inter relationship between chronic pain and depression

- Depression can present with chronic pain
- Chronic pain can cause depression
- Aches and pains may be symptoms of depression
- Chronic pain may be a variant of depression
- Depression can worsen chronic pain

Psychiatric management of chronic pain and depression

- Appropriate use of antidepressants
- Explaining the relationship between pain and depression
- Reattribution of pain to mood and depression
- Rehabilitation and living with pain

Use of antidepressants for chronic pain

- Elevation of mood
- Reduction of anxiety
- Potentiation of analgesics
- Primary analgesic effect
- Relief from nonorganic causes of pain
- Reduction in psychological symptoms such as restlessness, agitation, sleep disturbance.

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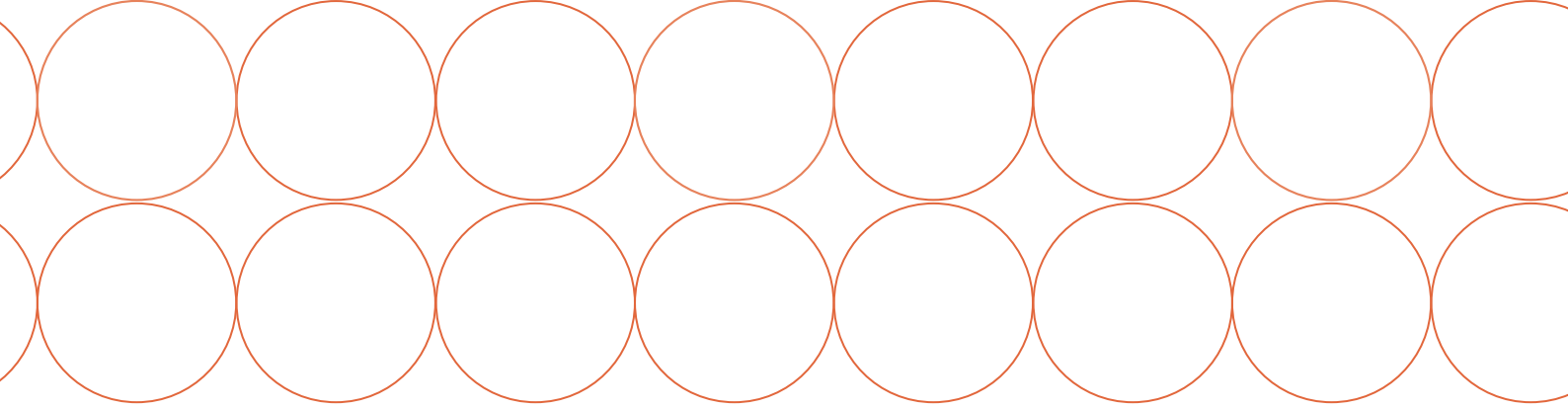

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Chapter 8

Depression and Human Immunodeficiency Virus

Francine Cournos, M.D., Karen McKinnon, M.A., and Mark Bradley, M.D.

IMPORTANCE OF IDENTIFYING AND TREATING DEPRESSION IN HIV-POSITIVE PATIENTS

Depression is common among people with human immunodeficiency virus (HIV) for a number of reasons. Depressive disorders may predispose individuals to engage in sexual and drug-use behaviours through which they may acquire or transmit HIV infection. Learning that one has a chronic, potentially fatal illness may precipitate the onset of depressive symptoms. HIV is a neurotropic virus that enters the central nervous system at the time of initial infection and persists there, and the virus itself may cause depressive symptoms. Studies show that depression is associated with reduced use of antiretroviral therapy, more rapid progression to AIDS, and early mortality.

HIGH PREVALENCE OF DEPRESSIVE DISORDERS AMONG HIV-POSITIVE PATIENTS

Rates of depression among people living with HIV have been estimated at 22% to 51%, with rates depending on the study methodology and population (Bing et al. 2001; Crane et al. 2007; Ickovics et al. 2001; Kolaric et al. 2006; Morrison et al. 2002; Penzak et al. 2000). Depression is the most common reason for psychiatric referral among people with HIV infections (Strober et al. 1997). Among patients infected with HIV who are referred for psychiatric evaluation, rates of major depression range from 8% to 67% (Acuff et al. 1999), and up to 85% of individuals who are HIV-seropositive report some depression symptoms (Stolar et al. 2005). Based on a meta-analysis of published studies, Ciesla and Roberts (2001) reported that people with HIV were almost twice as likely as those who were seronegative to be diagnosed with major depression, and that depression was equally prevalent in people with both symptomatic and asymptomatic HIV. Rates are generally lower among community-based samples of individuals who are HIV-positive and highest among intravenous drug users and women who engage in high-risk behaviours.

UNDERRECOGNITION AND UNDERTREATMENT OF DEPRESSION IN PATIENTS WITH HIV

In most places in the world, including the United States, psychiatric disorders are undertreated in HIV patients. For instance, nearly half of the sample in the HIV Cost and Services Utilization Study (HCSUS) screened positive for a psychiatric disorder, yet less than one-third of these individuals were taking psychotropic medication; this study also found significant disparities between African American subjects and others in the prescription of medication for depression (Bing et al. 2001). An increased focus on detection of depression is vital to improving the course of HIV illness.

Individuals with HIV/AIDs can be screening for depression using the criteria presented in Volume I, Chapter 3; however, somatic symptoms of depression are not the best guide for diagnosing depression in individuals with HIV because symptoms such as fatigue and insomnia are also very common in advanced HIV disease. Therefore, focusing on the more psychological manifestations of depression will result in more accurate assessment among people with HIV or AIDS.

DEPRESSION HAS NEGATIVE EFFECTS ON CLINICAL PROGRESSION AND MEDICAL OUTCOMES OF HIV DISEASE

Depression can occur at any time in the course of HIV infection (McDaniel and Blalock 2000), although the likelihood of depressive symptoms emerging is greater during pivotal points of the disease, such as initial positive HIV antibody testing, negative changes in immune status, and occurrence of opportunistic infections. Elevated rates of depression are seen among patients with more advanced HIV disease, particularly those hospitalised for medical illnesses (Goodkin et al. 1997). Depression is associated with increased

morbidity and mortality among those with HIV/AIDS (Antelman et al. 2007). In fact, depression has been shown to be associated with reduced immune response in HIV-positive patients (Alciati et al. 2006). A diagnosis of depression has been found to be associated with lower CD4 counts as well as with a more rapid decline in immune functioning and increased mortality (Sledjeski et al. 2005), even when the effects of medication adherence are controlled for (Bouhnik et al. 2005; Cook et al. 2004; Ironson et al. 2005). Both depressive symptoms and poor adherence are associated with shorter survival among individuals with HIV who are receiving highly active antiretroviral therapy (Lima et al. 2007).

DEPRESSION HAS NEGATIVE EFFECT ON ADHERENCE TO ANTIRETROVIRAL THERAPY AND OTHER TREATMENTS

Depression has been shown to be a robust predictor of nonadherence to HIV medications across a range of studies and methodologies (Boarts et al. 2006; Murphy et al. 2005; Palepu et al. 2004; Waldrop-Valverde and Valverde 2005). Depressed patients treated with antidepressants are more adherent to antiretroviral therapy than those with untreated depression, and demonstrate greater improvement in adherence after initiation of antidepressant treatment compared with untreated depressed patients over similar time intervals after their index diagnosis of depression (Cook et al. 2006; Yun et al. 2005). Fogel and Mor (1993) compared depressed and nondepressed patients with AIDS and found that depressed patients with AIDS were less likely initially to ask for help from a nursing home or accept the use of a respirator if needed; however, after treatment for depressive symptoms, they changed their minds. These research findings suggest that appropriate treatment for depression improves adherence to various kinds of medical care among depressed patients who are HIV-positive.

DEPRESSION HAS A NEGATIVE EFFECT ON BEHAVIOURS RELATED TO HIV TRANSMISSION AND PREVENTION

Negative affective states, particularly depression and anxiety, have been consistently associated with sexually risky behaviours, including those occurring during forced or transactional sex (Smit et al. 2006), among men who have sex with other men (Torres and Gore-Felton 2007), adolescents (Brown et al. 2006; Lightfoot et al. 2007), amphetamine injectors (Braine et al. 2006), and numerous other populations (Berg et al. 2007). Depression is specifically associated with a lower likelihood of condom use and proper condom use (Hong et al. 2007).

DEPRESSION AND SUICIDE RISK IN HIV/AIDS

Suicidal ideation among HIV-positive individuals is relatively common (19%) and is associated with symptoms of depression (Carrico et al. 2007). The risk of suicide, which was previously documented to be 16 to 66 times greater in patients with AIDS than in the general population (Maj et al. 1993), remains high even as HIV infection and AIDS are being treated as chronic conditions.

Clinical Vignette

Ms. D., a 65-year-old woman diagnosed with HIV 14 years earlier, has a long history of depression. She made a suicide attempt by overdose 8 years ago after her cousin, with whom she had been close since childhood, died from AIDS-related pneumonia. Although currently not actively suicidal, she reports ongoing feelings that things would be better if she could "just disappear."

COMMON RISK FACTORS FOR DEPRESSION IN HIV/AIDS

Risk factors for depression include a history of depression, substance abuse, unemployment, lack of social support, use of avoidance coping strategies, HIV-related physical symptoms, and multiple losses (Goodkin et al. 1997).

DEPRESSION AND COMMON MEDICAL COMORBIDITIES IN HIV/AIDS

More often than not, HIV co-occurs with other conditions such as tuberculosis (particularly in developing countries) and hepatitis C (HCV) (world-wide); such conditions are readily identifiable through medical tests that are routinely offered to people living with HIV. Medications used to treat concomitant conditions such as HCV are associated with depressive symptoms in patients with HIV/AIDS. Approximately 20%–30% of patients treated with pegylated interferon and ribavirin report depression during therapy (Fried 2002), so that it is important to identify patients who had pre-existing depression as well as to monitor all patients being treated with this regimen (see Bartlett and Gallant 2007, for a fuller description of the implications of HCV treatment for depression).

COMMON PSYCHIATRIC COMORBIDITIES

Comorbid psychiatric conditions are common among individuals who have depression and HIV, but HIV care providers often have difficulty recognising and helping their patients manage these psychiatric problems. In developed countries, substance use disorders are the most common co-occurring psychiatric disorders among people with depression and HIV/AIDS, Individuals with dual psychiatric and substance use disorders may be at higher risk for HIV infection than those with either disorder alone (Ferrando and Batki 2000). For instance, based on data from the HCSUS study, it was estimated that 13% of the sample had co-occurring psychiatric symptoms and either or both drug dependence symptoms or heavy drinking (Galvan et al. 2003). Sixty-nine percent of those with a substance-related condition also had psychiatric symptoms; 27% of those with psychiatric symptoms also had a substance-related condition. Thus, in clinical settings of any kind it is prudent to screen patients with one type of psychiatric disorder for other psychiatric disorders.

Clinical Vignette

Mr. K is a 45-year-old man with AIDS with a history of mood and psychotic symptoms since his twenties. During his late thirties and early forties, he used crack cocaine daily, and experienced severe ongoing paranoia, hallucinations, depression, and social withdrawal. For the past 2 years, he has been abstinent from crack, and although he continues to have some overvalued ideas and somatic preoccupations, he is free from hallucinations and delusions, and enjoys substantially improved social functioning.

DIFFERENTIAL DIAGNOSIS

Diagnosing depression in HIV requires a careful differential diagnosis to rule out treatable medical disorders. Depression must be distinguished from grief, demoralisation, and the apathy associated with dementia. Depression and cognitive impairment often co-exist and depression should be treated under those circumstances. It is also essential to rule out intoxication or withdrawal (Bartlett and Gallant 2007).

Distinguishing somatic symptoms of depression from somatic symptoms related to HIV illness and its treatment can also be challenging. For example, it may be more important to focus on anhedonia, guilt, and suicidal ideation than on disturbances of sleep and appetite. Fatigue and depression are among the most frequently reported symptoms of people with HIV/AIDS, and patients seeking help for fatigue and/or depression should always be evaluated for both symptoms (Voss et al. 2007).

As Bartlett and Ferrando (2006) have outlined, neuropsychiatric complications of the direct effects of HIV in the brain become more frequent as illness advances. Common problems include decreased attention and concentration, psychomotor slowing, reduced speed of information processing, executive dysfunction, and, in more advanced cases, impairment of verbal memory. The severity of neuropsychiatric manifestations ranges from subclinical to specific disorders that include, most commonly, minor cognitive-motor disorder (MCMD) and HIV-associated dementia (HAD). Psychiatric illnesses associated with HAD, in which symptoms range from apathy and depression to mania and psychosis, mimic functional psychiatric disorders and require a thorough differential diagnosis, eliminating all other possible medical causes, including opportunistic infections, metabolic problems, side effects of antiretroviral agents, and substance intoxication or withdrawal.

Clinical Vignette

Ms. J is a 32-year-old woman without significant medical or psychiatric history who presents to the ER for cough, fever, and weight loss. The psychiatric consult service is called because the patient's notably flat affect and limited speech output lead the primary team to believe she is severely depressed, although she states her mood is fine. Magnetic resonance imaging of the brain reveals a large frontal ring-enhancing lesion consistent with CNS toxoplasmosis or lymphoma.

PRESCRIBING ANTIDEPRESSANTS IN HIV/AIDS TREATMENT

Patients with HIV infection who are asymptomatic and not receiving antiretroviral therapy can be treated for depression in much the same way as patients without medical illness. Patients with advanced HIV infection are often more sensitive to medication side effects. Drug interactions become a consideration when patients are taking antiretroviral therapy or treatments for other associated diseases. In many resource-poor countries, this includes treatment of tuberculosis.

The evidence base on which to base decisions about antidepressant treatment in patients with HIV/AIDS is limited because few well controlled trials that included a significant number of patients have been conducted. Smaller studies of antidepressants conducted with varying degrees of rigor and at various stages of HIV illness have demonstrated efficacy for many of the tricyclic antidepressants, all of the common selective serotonin reuptake inhibitors (SSRIs), mirtazapine, bupropion, and dextroamphetamine (Cozza et al. 2008).

The major concerns when prescribing antidepressants to medically ill patients and/or those taking HIV-related medications are drug interactions and overlapping toxicities. The latter is especially worrisome in patients with pre-existing liver disease, often from alcohol misuse and/or HCV infection. With regard to drug interactions with antiretroviral therapy, the greatest concern arises with respect to patients taking protease inhibitors, especially ritonavir and ritonavir-boosted medications. Ritonavir is a moderately strong CYP2D6 inhibitor and decreases desipramine clearance by 59%, causing higher than anticipated blood levels (von Moltke et al. 1998). This is one of the few available in-vivo studies concerning drug interactions between antidepressant and antiretroviral agents.

Most drug interactions are predicted theoretically, and results may differ in practice. As noted above, the risk of drug interactions is most significant with protease inhibitors and includes concerns about elevated blood levels of many antidepressants with associated toxicity (Wainberg et al. in press). In general, in initiating antidepressant treatment in a patient receiving protease inhibitors, it is best to start low and slowly raise the dose of any antidepressant medication. Although it is less common, certain protease inhibitors may decrease levels of particular antidepressants. For example, lopinavir/ritonavir reduces levels of bupropion (Hogeland et al. 2007). As can be seen from the specificity of this example, it is best to consult online resources to check for potential drug interactions since the number of new antiretroviral agents keeps growing and it is impossible to memorise all their potential interactions with psychotropic medications.

As with many other medical illnesses, some antidepressants may be useful because of their side effect properties. Insomnia is common in patients with AIDS, and sedating antidepressants may be helpful for patients with this problem. Neuropathic pain is also common and may be helped by tricyclic antidepressants. Thus, a consideration of the patient's somatic symptoms can sometimes guide the choice of the best antidepressant.

Testosterone deficiency in both men and women is also common among HIV/AIDS patients and can cause considerable fatigue and other somatic symptoms that may be confused with depression. It is important to check for and correct this deficiency if at all possible.

OTHER EFFECTIVE TREATMENTS FOR DEPRESSION IN PATIENTS WITH HIV/AIDS

Certain brief psychotherapies, such as interpersonal psychotherapy and cognitive behavioural therapy, as well as psychoeducational programs have shown good results in treating depression and enhancing coping in resource-poor countries where antidepressants may not be readily available for people living with HIV (Bolton et al. 2003; Olley, 2006). In developed countries, where patients with HIV are frequently taking multiple medications, having such non-medication options can be desirable.

CONCLUSIONS

Screening and provision of psychosocial and medication interventions for depression should be part of comprehensive HIV care. Primary care efforts to improve outcomes in the course of HIV disease should include effective management of psychiatric conditions, including depression, since successful intervention for these conditions may reduce the risk of morbidity and mortality in HIV/AIDS. Addressing depression in patients with HIV may result in better treatment outcomes, enhanced quality of life, and decreased HIV transmission.

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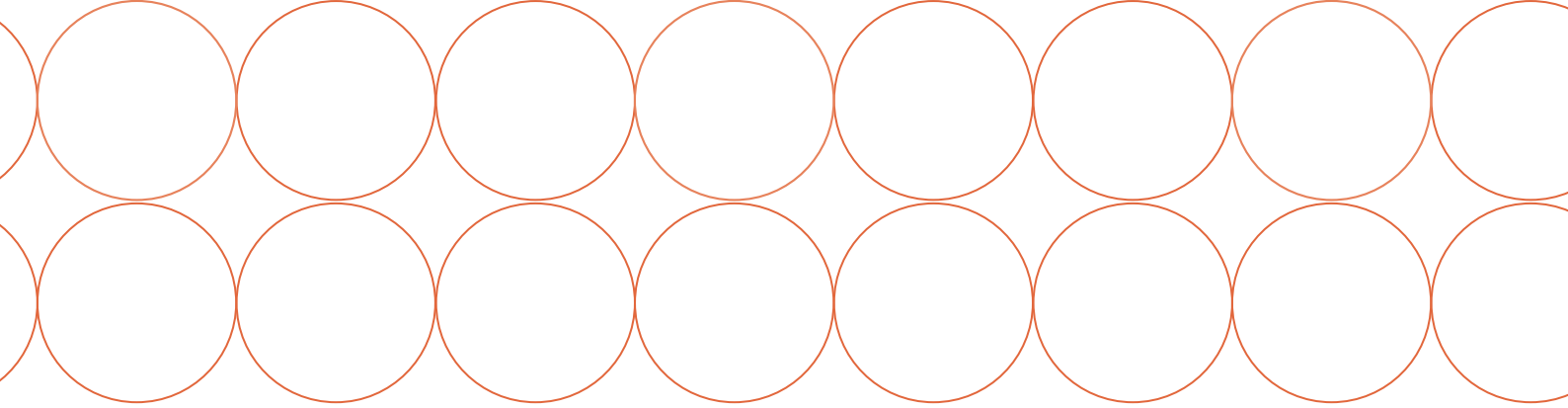

9

Chapter 9

Depressive Disorders and Pain

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THE RELATIONSHIP BETWEEN DEPRESSION AND PAIN

Pain is a complex, multidimensional construct that involves not only patients' physical and nociceptive experiences but also their personalities, affect, cognition, behaviours, and social relations (Breitbart and Holland, 1990; Stiefel 1993). The International Association for the Study of Pain (IASP) defines pain as an "unpleasant sensory and emotional experience associated with actual or potential tissue damage, or described in terms of such damage" (IASP Task Force on Taxonomy 1994). Because of its emotional component, pain is conceptualised as subjective, and it is therefore vulnerable to fluctuations when there are changes in mood, including the onset of depressive disorders.

A substantial body of research has demonstrated the reciprocal relationship between psychological factors and pain (Breitbart and Holland 1990; Massie and Holland 1987). While the relationship between depressive disorders and pain has been well established, the manner in which they interact is often complicated. Psychological factors and beliefs about the meaning of pain have an impact on patients' perception of pain intensity (Daut and Cleeland 1982; Spiegel and Bloom, 1983b; Syrjala and Chapko 1995). The presence of pain can also influence the onset and severity of depressive symptoms (Mystakidou et al. 2006, 2007b; Serlin et al. 1995). Studies suggest that the extent to which pain interferes with functioning has more of a negative impact on mood than does the severity of pain (Mystakidou et al. 2006, 2007b; Serlin et al. 1995). Pain and depression, when they occur in combination, may be more resistant to treatment, because each can prolong the other (Gallagher and Cariati 2002). Thus, effective management of pain often requires a multimodal intervention (Breitbart and Holland 1990). This chapter reviews strategies for assessing and treating depressive disorders in patients reporting pain of various aetiologies.

PREVALENCE OF COMORBID PAIN AND DEPRESSION

The presence of pain is associated with increases in both depressive symptoms and diagnoses of major depression. Approximately 30% of patients suffering from persistent pain also develop clinical depression related to their pain (Gallagher and Cariati 2002). A World Health Organization (WHO) study showed that patients with chronic pain are four times more likely to meet clinical criteria for an anxiety or depressive disorder than those without significant pain (Gureje et al. 1998). Specifically, mood disorders have been observed in 46% of patients with chest pain, 43% of patients with abdominal pain, 40% of patients with headache, 38% of patients with back pain, and 34% of patients with joint or limb pain (Kroenke et al. 1994). In fact, researchers have referred to the interacting phenomena of pain and depressive symptoms as a single "depression-pain syndrome" (Lindsay and Wyckoff, 1981). Likewise, patients with more severe depressive symptoms are more likely to report pain: over 50% of patients suffering from depressive disorders experience substantial pain, including headache; abdominal, thoracic and pelvic pain; facial, neck and back pain; and pain in extremities (Corruble and Guelfi 2000; Larson et al. 2004; Lindsay and Wyckoff 1981; Skevington 1983; von Knorring et al. 1983). Table 9.1 lists a number of symptoms shared by chronic pain and depression.

Several medical illnesses, such as cancer, multiple sclerosis, fibromyalgia, arthritis, human immunodeficiency virus (HIV), chronic back pain, irritable bowel syndrome, and headaches, commonly result in painful physical symptoms and an increased risk of depression (Breitbart 1990; Breitbart and Dibiase 2002; Henningsen et al. 2003; Patten 2001; Wolfe 1999). For example, patients with cancer who report pain appear to be

at greater risk for developing psychiatric disorders (primarily adjustment disorder with depressed or anxious mood and major depression) than patients without significant pain (Ahles et al. 1983; Miovic and Block 2007; Woodforde and Fielding 1970). In turn, the presence of emotional distress is associated with increased cancer pain, especially in late stages of the disease (Mystakidou et al. 2007b; Teunissen et al. 2007; Wilson et al. 2007). Pain management is similarly a critical component of maintaining the well-being of patients with HIV and AIDS, especially as treatment advances in the past decade have substantially increased patients' life expectancies. Recent estimates of the prevalence of pain among individuals infected with HIV have ranged from 30% to over 90%, with higher rates in the latest stages of illness (Breitbart and Dibiase 2002). The profound impact of pain on quality of life was demonstrated by Rosenfeld et al. (1996), who found that the presence and intensity of pain was significantly associated with depressive symptoms among ambulatory patients with AIDS.

Estimates of depression among patients with chronic pain, internationally recognised as a syndrome in its own right (Bonica 1953), have ranged between 22% and 87% (Benjamin et al. 1988; Giesecke et al. 2005; Lindsay and Wyckoff 1981; Manchikanti et al. 2002; Reich et al. 1983). While depression is usually believed to be a consequence of chronic pain rather than a cause, studies have shown that psychosocial factors increase the risk of developing chronic pain disorders (Atkinson et al. 1991; Gatchel and Dersh 2002; Picavet et al. 2002). Among individuals living with fibromyalgia, a chronic illness characterised by widespread pain, tenderness, and fatigue, 34% to 62% will experience comorbid depression during their lifetime (Ahles et al. 1991; Arnold et al. 2006).

TABLE 9.1

Common symptoms shared by chronic pain and depression

Sleep disturbance
Mood symptoms (anxiety, irritability, decreased pleasure, sadness)
Family stress
Reduced sexual activity
Reduced physical activity/exercise
Decreased self-esteem
Financial stress
Vocational issues
Legal concerns
Fear of injury

Source: Turk et al. 2002

COMMON ETIOLOGIES AND PATHWAYS

Despite the convincing evidence of an interactive relationship between pain and depression, researchers have been challenged to identify a dominant causal or antecedent pattern. Pain may precipitate depression, and vice versa. Chronic pain clearly can result in functional and social disabilities that may compromise a patient's sense of personal mastery, self-esteem, enjoyment, and concentration (Leino and Magni 1993; Rudy et al. 1988), which may contribute to the onset of depression. Prospective research has also suggested that depression may lead to later physical pain syndromes, including chronic musculoskeletal disorders, headaches, and chest pain (Currie and Wang 2005; Magni et al. 1994; Von Korff et al. 1993).

There is notable overlap in the physiological mechanisms and brain regions involved in both pain and depression (Rome and Rome 2000). Von Korff and Simon (1996) proposed two possible frameworks for understanding the interaction of pain and depression: 1) certain individuals are genetically vulnerable to both physical and psychological symptoms, and being prone to distress amplifies physical discomfort; 2) the stress of substantial pain elicits or exacerbates psychological symptoms. The "gate control theory of pain" is a longstanding and popular conceptualisation of how the interaction between emotional and physical factors affects pain perception (Melzack and Wall 1965). It proposes that nociception (i.e., pain) is "gated" by the spinal cord according to the type of nerve fibres carrying the pain signals, by non-nociception stimuli front the body, and by signals that descend from the brain to the spinal cord and inhibit or enhance incoming nociception information (Melzack and Wall 1965). Other theories of pain and depression emphasise neurobiological and biobehavioural processes, such as corticolimbic sensitisation and kindling (Rome and Rome 2000). Pain can also act as a neurobiological antecedent for depression. For example, prolonged pain leads to structural changes in the central nervous system that increase vulnerability to chronic pain, which in turn can exacerbate stress and trigger chemical changes that contribute to the onset of depressive syndromes (Gallagher 1999). Furthermore, serotonin and norepinephrine are neurotransmitters that play a role in both mood disorder symptoms (Delgado et al. 1990, 1999) and in the brain's pain-modulating circuit (Sawynok and Reid 1996). These neurotransmitters enhance endogenous pain-suppressing functions (Sawynok and Reid 1996). A meta-analysis of controlled treatment trials demonstrated that antidepressants provide significant relief from the painful symptoms of fibromyalgia, headache, idiopathic pain, tinnitus, and gastrointestinal syndromes (O'Malley et al. 1999). Likewise, when serotonin and norepinephrine are blocked, antidepressant-mediated pain relief is inhibited (Mico et al. 1997; Schreiber et al. 1999).

ASSESSMENT ISSUES AND RISK FACTORS

Both depression and pain are uniquely associated with a variety of risk factors and outcomes, and these associations may be strengthened when depression and pain co-occur. Personality disorders and maladaptive coping styles have frequently been observed among patients with chronic pain (Geisser 2004; Weisberg and Vaillancourt, 1999). Among primary care patients, the number of different pain sites may be the strongest predictor of depression (Von Korff and Simon 1996). In studies of patients with cancer, depression and pain have been related to distinct psychosocial factors such as hopelessness (Mystakidou et al. 2007a), more impaired cognitive functioning (Rodin et al. 2007a), and desire for hastened death (Chochinov et al. 1995; Mystakidou et al. 2007a; Rodin et al. 2007b). Sleep disturbances (Sela et al. 2005), poorer occupational functioning, and decreased quality of life are also related to comorbid depression and pain (Bair et al. 2003). Management of depression and pain is complicated because low mood can have a negative impact on adherence to pain management regimens and increase the risk for nonadherence to or abuse of medications (DiMatteo et al. 2000; Gallagher 1999). It is particularly important for clinicians to remain aware of the heightened risk for suicidality among patients experiencing depression and pain (Breitbart 1987, 1990; Sison et al. 1991) and to provide aggressive treatment and close monitoring when both of these risk factors are present.

Case Vignette: Interaction between Pain and Depressive Symptoms

Mrs. S is a married 57-year-old female advertising executive with a history of recurrent major depression. She has experienced several episodes of depression since the initial onset of the illness in her twenties and had a moderate response to a combination of antidepressants and long-term psychotherapy. Mrs. S was diagnosed with cervical cancer 4 years ago and was treated with surgery and chemotherapy. Her disease was in remission until a recent recurrence that involved metastases to her pelvic bone, liver, and brain. When Mrs. S began experiencing growing pain in her pelvic region, she found herself feeling increasingly hopelessness about her circumstances. She even occasionally had thoughts that she would rather die than go on like this. She avoided discussing her concerns about her pain and future functioning with her doctor and family. She assumed her depression was recurring and would eventually pass. Within a week, Mrs. S began to have difficulty walking comfortably because of the pelvic discomfort. Her husband became very concerned about her increasing impairment as well as the intensity of her pain and encouraged her to call her oncologist. Mrs. S reported her symptoms at her next visit, and her oncologist provided her with several options for pain management and with a referral for a psychiatrist specialising in psycho-oncology. Mrs. S began regularly taking analgesics and met with the psychiatrist, who prescribed duloxetine because of its potential for alleviating both pain and depressive symptoms. Within 4 weeks, Mrs. S reported a substantial decrease in physical pain and a lift in her mood, allowing her to enjoy spending time with her family and reengage in meaningful activities.

DIFFERENTIATING MOOD DISORDERS AND PAIN

Diagnosing depression in patients with pain due to a medical condition is often challenging because of the overlap between the somatic symptoms of their disease and those resulting from the depressive syndrome. Despite the fact that half of all those who are high consumers of medical care suffer from psychological distress (Katon et al. 1990), it appears that primary care patients presenting with pain are less likely to be recognised as depressed, the most common type of distress reported. An estimated 50% of patients with major depression are never diagnosed by their primary care physician (Simon and VonKorff 1995), and depressed patients with pain, who use medical services intensively, make relatively little use of mental health services (Bao et al. 2003). Consequently, these patients frequently do not receive appropriate and adequate treatment.

Optimal assessment of depression involves a thorough diagnostic interview. However, the use of self-report measures or visual analogue scales, such as the Distress Thermometer (Patrick-Miller et al. 2004), can also provide helpful supplemental information. When full assessment is not feasible, gross evaluations of depression and pain may be useful in identifying patients who may need further evaluation or treatment (Bruera et al. 1991; Chochinov et al. 1994). In patients with debilitating disease, careful consideration must be given when patients endorse anhedonia, one of the two core symptom criteria of depression, because patients with physical illnesses often experience a functional decline that restricts their ability to participate in activities. When a loss of interest in activities appears to be pervasive, however, and includes disinterest in interacting with family and friends, then it meets symptom criterion for depression (Lynch 1995; Passik and Breitbart 1996). Unexplained somatic pain (including headaches, gastrointestinal pain, and back pain) frequently serve as culturally sanctioned idioms of distress in patients meeting clinical criteria for depression. In such cases, psychological symptoms can usually be found through adequate and sensitive probing. Since this practice is rare in primary care settings, depression is likely to be globally underdiagnosed (Bhugra and Mastrogianni 2004). Nevertheless, clinicians should be careful not to become overly reliant on psychological variables to explain continued pain or lack of response to therapy when medical factors have not been adequately addressed.

CULTURAL CONSIDERATIONS

Researchers have traditionally asserted that patients in non-Western countries are more likely to report somatic symptoms and to deny psychological symptoms than their Western counterparts (Bhatt et al. 1989; Escobar 2004; Mezzich and Raab 1980). This phenomenon is often attributed to cultural stigma against psychiatric diagnoses. For example, in many parts of Chinese society, epidemiological research has revealed that a diagnosis of depression is seen as "morally unacceptable and experientially meaningless" and that patients often endorse symptoms of discomfort, "feelings of inner pressure", pain, and fatigue without acknowledging sadness or despair (Kleinman 2004). Notably, a recent review of community surveys and clinical studies challenged the generalisation of such findings by demonstrating that psychological and somatic symptoms were similarly balanced in non-Western and Western nations (Simon et al. Ormel, 1999). Researchers have since begun to investigate other predictors of disparate rates of depression diagnosis around the world.

Analysis of WHO data on 5,447 primary care patients who were evaluated for depressive and somatoform disorders in 14 countries (5 continents) showed that 45%–95% of those meeting criteria for major depression only reported somatic symptoms (Simon et al. 1999). Of those patients who were depressed, 11% denied psychological depressive symptoms when directly questioned. Somatic presentations were more common in patients who did not have an ongoing relationship with a primary care physician, suggesting that in addition to cultural differences, characteristics of available health care systems may significantly influence whether depressed patients endorse more than somatic symptoms (Simon et al. 1999).

The experience and expression of pain have also been found to vary across racial, ethnic, and gender groups within a given society (Green et al. 2003; McCracken et al. 2001; Richards et al. 2000). It is important to note that race and ethnicity designations sometimes serve as a proxy for socio-economic status, which is itself a powerful predictor of disability, pain experience and expression, and health care access (Fillingim 2004; Green et al. 2003). The impact of ethnic and cultural factors can also be mediated by health care professionals' responses and barriers to communication (Bonham 2001; Davidhizar et al. 2004).

TREATMENT OF PAIN AND DEPRESSION

The use of psychiatric interventions in the treatment of patients with pain has become integral to a comprehensive clinical approach (Breitbart 1989; Breitbart and Holland, 1990; Foley 1975, 1985; Massie and Holland 1987). Concurrent treatment of depression and pain may be justified because they share some common biological mechanisms (Bair et al. 2003). However, successful symptom management is also dependent on disentangling and addressing both the physical and the psychological issues underlying each patient's pain to the extent that it is possible to do so. Applying psychosocial and somatic therapies in conjunction can lead to reciprocal effects. Treatments targeting psychological variables can have a profound impact on nociception, and therapies directed at pain detecting neurons can improve psychological aspects of the perception and experience of pain.

Pharmacological Interventions

Pharmacotherapy is often a central component of treatment for the depressed patient with pain. When possible, the first line of treatment should be to attempt to achieve adequate pain management with analgesics. Because depressive symptoms may resolve once pain dissipates, mood should then be re-evaluated before proceeding with treatment. Depressed patients who report significant pain may benefit from treatment with psychopharmacological agents that have analgesic properties. Several antidepressants have antinociceptive effects, most notably the tricyclic antidepressants (TCAs); venlafaxine, a serotonin-norepinephrine reuptake inhibitor (SNRI); and bupropion, which inhibits reuptake of norepinephrine and dopamine (Raison and Miller 2003). Because TCAs and tetracyclic antidepressants require more time to take effect and often result in unfavourable side effects, selective serotonin reuptake inhibitors (SSRIs), which also have the advantage of dosing simplicity, are often initially recommended. However, there is not a great deal of empirical support for the efficacy of SSRIs in relieving pain. For patients who do not respond to SSRIs, SNRIs are sometimes preferred (Gallagher 1999). The SNRI duloxetine has been shown in recent studies to alleviate pain among fibromyalgia patients with and without a diagnosis of depression (Arnold et al. 2004).

Second line treatments include trazodone, a highly serotonergic antidepressant that may be useful in reducing pain symptoms (Costa et al. 1985). Mianserin (available in select countries), a serotonergic tetracyclic antidepressant with adjuvant analgesic properties that is used widely in Europe and Latin America (Schifano et al. 1990), appears to be safe and effective in treating depression among cancer patients (Costa et al. 1985). Among the available monoamine oxidase inhibitors (MAOIs), phenelzine has been shown to have adjuvant analgesic properties in patients with atypical facial pain and migraine (Anthony and Lance 1969; Lascelles 1966). Because the use of MAOIs in combination with opioid analgesics have been associated with myoclonus and delirium, caution is needed if these agents are used in combination (Breitbart 1988).

Psychostimulants are not only rapidly effective as antidepressants (Orr and Taylor 2007), but they are also helpful in reducing excessive sedation secondary to use of opioid analgesics. Methylphenidate (Bruera et al. 1987, 1989, 1992), dextroamphetamine (Forrest 1977), and mazindol (Bruera et al. 1986) have all been shown to decrease pain symptoms. Benzodiazepines are generally not believed to have analgesic properties, although they are potent anxiolytics and anticonvulsants (Coda et al. 1992); alprazolam has mild antidepressant

properties and clonazepam may be useful in treating neuropathic pain (Caccia 1975; Swerdlow and Cundill 1981). Hydroxyzine, an antihistamine, is a mild anxiolytic with sedating and analgesic properties (Rumore and Schlichting 1986). There is also evidence that atypical antipsychotics, such as olanzapine, may be efficacious in decreasing cancer pain (Khojainova 2002), fibromyalgia (Freedenfeld et al. 2006), and chronic pain (Gorski and Willis 2003). Other antipsychotics with analgesic properties include quetiapine, risperidone, and ziprasidone (Calandre et al. 2007; Fishbain et al. 2004). Some of these antipsychotic agents have also been show to reduce depressive symptoms, including sadness, in various populations (Calandre et al. 2007; Davis et al. 2002).

Psychosocial Interventions

Several forms of psychotherapy have been empirically validated, both alone and in combination with psychopharmacological treatment, in the treatment of comorbid pain and depression (Fava et al. 1998; Sonawalla and Fava 2001; Thase et al. 1997). The most effective psychosocial treatments that address both depressive and pain symptoms have common goals of providing emotional support, psychoeducation, assistance with adaptation, coping strategies, problem solving, and communication skills. Empirically supported treatments for pain and depression include cognitive-behavioural therapy (Levitan 1992; Syrajala et al. 1992), acceptance and commitment therapy (Dahl et al. 2004; Hayes et al. 2006), relaxation, guided imagery, self-hypnosis (Levitan 1992; Montgomery et al. 2000; Spiegel and Bloom 1983a), biofeedback (Erickson 2005; Turk et al. 1993), supportive psychotherapy (Turk et al. 2002), and family interventions (Turk et al. 2002). Music and art therapy may also be useful (Cassileth et al. 2007; Deng and Cassileth 2005). A number of interventions for patients with pain and depression that are appropriate for use in primary care settings are listed in Table 9.2.

TABLE 9.2

Appropriate interventions for primary care settings

Find a support network through family, friends, and participation in community support forums
Seek out reputable sources of information, including books, organizations and online sources
Maintain a diary to record changes in pain, emotions, and medication use
Yoga, stretching, and/or other gentle physical exercises
Relaxation techniques, biofeedback, hypnosis, and guided imagery to manage stress
Physical/ occupational therapy

Source: Gallagher and Cariati 2002

Complementary Treatments

The use of complementary and alternative medicine (CAM) has become increasingly popular among patients as a treatment choice in conjunction with or instead of more traditional treatment methods. While such approaches are often considered first-line treatments in Eastern cultures, in Western medicine, clinicians still tend to recommend them when conventional treatments fall short of relieving symptoms or lead to uncomfortable side effects. Massage has demonstrated positive effects on both depression and pain in patients with various conditions, including fibromyalgia, bone marrow transplantation, and cancer (Ahles et al. 1999; Cassileth and Vickers 2004; Field et al. 2002). Acupuncture has been widely used to alleviate acute and chronic pain of various aetiologies, with encouraging results (Melchart et al. 1999; Sator-Katzenschlager et al. 2004; Trinh et al. 2004). In a recent randomised controlled trial, acupuncture

Case Vignette: Impact of Psychosocial Approaches on Pain Management

Mr. B is a 49-year-old man who has chronic, debilitating back pain. He has tried numerous non-surgical treatment approaches, including over-the-counter drugs, prescription analgesics, acupuncture, cortisone injections, and frequent chiropractic adjustments, without success. Mr. B eventually had surgery as a "last resort" to relieve pressure on nerve roots in his spine, but he perceived little relief from the procedure. Prior to the onset of back pain during his late thirties, Mr. B had been a carpenter who enjoyed physically challenging work and the outdoors and typically had a positive attitude toward adversity. As the years passed and his pain did not improve, he became increasingly frustrated, irritable, and anxious. Mr. B gave up on returning to work and began collecting disability. During a recent visit with his new primary care physician, Mr. B reported his psychological symptoms. The doctor diagnosed Mr. B. with major depressive disorder and referred him to a psychologist specialising in cognitive-behavioural therapy. The therapist helped the patient to manage his pain through relaxation, to challenge his depressive cognitions that "nothing helps", and to engage in more pleasurable and meaningful activities. As Mr. B's depressive symptoms began to remit, he resumed hobbies that did not require physical exertion and began to socialise more. He also reported decreased pain intensity. While his pain was still frequently present, Mr. B was finally able to perceive his symptoms as manageable and was better able to cope with stressors related to his physical condition.

was shown to reduce cancer pain intensity by 36% 2 months post-intervention, demonstrating a significant improvement over two placebo conditions (Alimi et al. 2003). Conceptualised as a mind-body treatment, acupuncture has also demonstrated efficacy in improving mood symptoms, with some researchers suggesting that traditional and electro-acupuncture can be as effective as psychopharmacological agents in the treatment of depressed patients (Han et al. 2004; Luo et al. 1998).

Homeopathic remedies with their origin in Eastern medical traditions are also frequently used and result in high levels of patient satisfaction (Goldstein and Glik 1998). St. John's Wort, one of the most frequently studied alternative treatments, has proven superior to placebo in randomised clinical trials for treating mild to moderately severe depressive disorders (Linde et al. 1996). Research examining its efficacy in comparison to psychopharmacological treatments has been mixed, however (Linde et al. 2005). Clinical trials have not provided strong support for arnica, a popular herbal analgesic, although researchers have noted serious methodological limitations in studies of homeopathic medicine (Linde et al. 2001). An increasing number of physicians recommend the use of B vitamins, omega-3 fatty acids, inositol, and S-adenosyl methionine (SAM-e) to treat mood disorders (Brown and Gerbarg 2001). Attention has focused particularly on SAM-e, which has been found in clinical trials to be superior to placebo and as effective as TCAs in relieving symptoms of depression (Alpert et al. 2004; Mischoulon and Fava 2002). SAM-e also appears to have a faster onset of action than conventional antidepressants and may aid in potentiating the effect of tricyclic antidepressants (Mischoulon and Fava 2002). Because of the potentially serious negative consequences of dietary supplements, especially when used in conjunction with mainstream medications, practitioners should thoroughly interview patients regarding their self-care practices. Overall, however, the evidence base for most of these homeopathic treatments is still very limited (Pilkington et al. 2005).

OTHER TREATMENT ISSUES

Early Intervention

Optimal treatment for comorbid pain and depression is administered preventatively or involves early intervention, when lower doses of medications are required to manage symptoms and treatments are often more effective. Care providers who are able to evaluate psychosocial risk factors that influence the onset of symptoms and comorbid disorders that contribute to chronic disability can often spare patients significant suffering from their mood or pain-related illness (Boersma and Linton, 2005; Picavet et al. 2002). The risk factors discussed earlier in this chapter can serve as guidelines for identifying patients who may benefit from prophylactic treatment.

Barriers to Adequate Treatment

All too frequently, psychological variables are proposed to explain continued pain or lack of response to therapy, when in fact medical factors have not been adequately assessed or considered. Some potential causes for this problem include lack of training of clinicians in recognition, assessment, and evaluation of both pain and depression; lack of knowledge of current pharmacy or psycho-therapeutic approaches; focus on prolonging life rather than alleviating suffering; lack of communication between doctor and patient; limited expectations of patients for achieving pain relief; limited capacity of patients impaired by organic mental disorders to communicate; lack of availability of narcotics; physicians' fear of causing respiratory depression; and, most importantly, doctors' fear of increasing addiction and substance abuse (Breitbart 1989; Cleeland et al. 1994; Foley 1985; Twycross and Lack 1983). Especially in the context of advanced illnesses, psychological distress in patients with pain must initially be assumed to be the consequence of uncontrolled pain. Personality factors may be quite distorted by the presence of pain, and relief of pain often results in the disappearance of what was perceived as being a psychiatric disorder (Cleeland and Tearnan 1986; Marks and Sachar 1973).

SUBSTANCE ABUSE

Addiction to a prescribed medication may be characterised by cravings, physical tolerance, and overwhelming involvement in obtaining and using it for effects other than pain relief. Studies of the patterns of chronic opioid analgesic use in cancer patients have demonstrated that, although tolerance and physical dependence commonly occur, addiction is rare and almost never occurs in an individual without a history of drug abuse that predates the physical illness (Kanner and Foley 1981). Instead, an increase in the use of opioid analgesics is typically related to increases in pain severity due to the progression of disease. The fear of addiction can affect patient adherence to and physician management of pharmacotherapy and, therefore, increases the risk of under-medicating pain (Breitbart and Holland 1990; Charap 1978; Twycross and Lack 1983). When a patient does have an active addiction, particularly if it involves opioids or is comorbid with another psychiatric disorder, the management of pain can be quite challenging. Specialised substance abuse consultation services may be helpful in the team approach to these patients.

CONCLUSION

Assessment and treatment of depression and pain are essential components of quality care for medically ill patients, yet both depression and pain typically remain under-recognised by treatment providers. The interaction between depression and pain can make this process rather complex and additional training in recognition and treatment may be necessary. Ultimately, treatment of both depression and pain will reduce distress and suffering among patients and improve quality of life.

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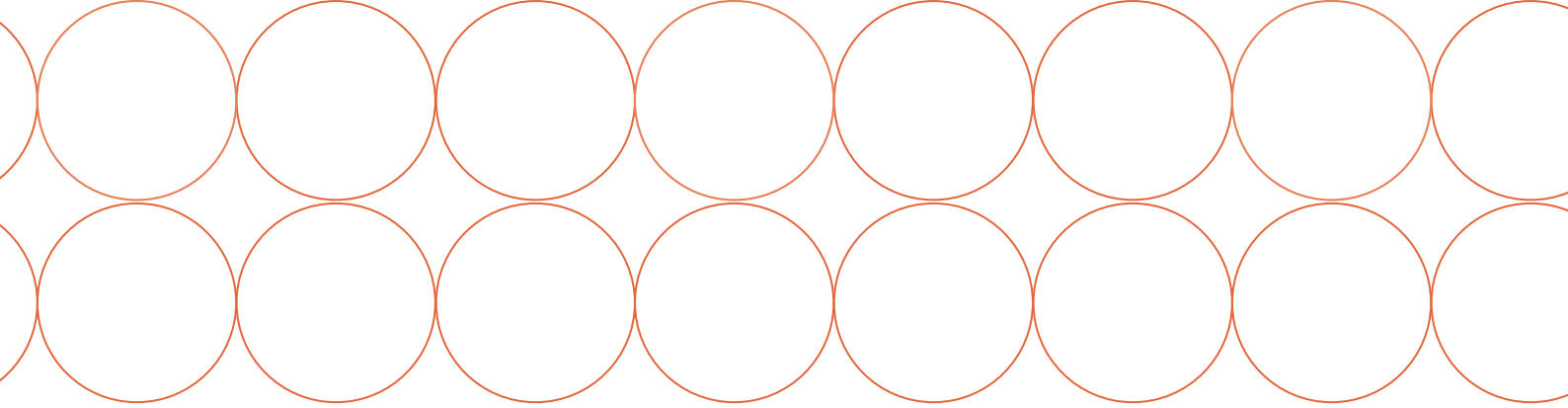
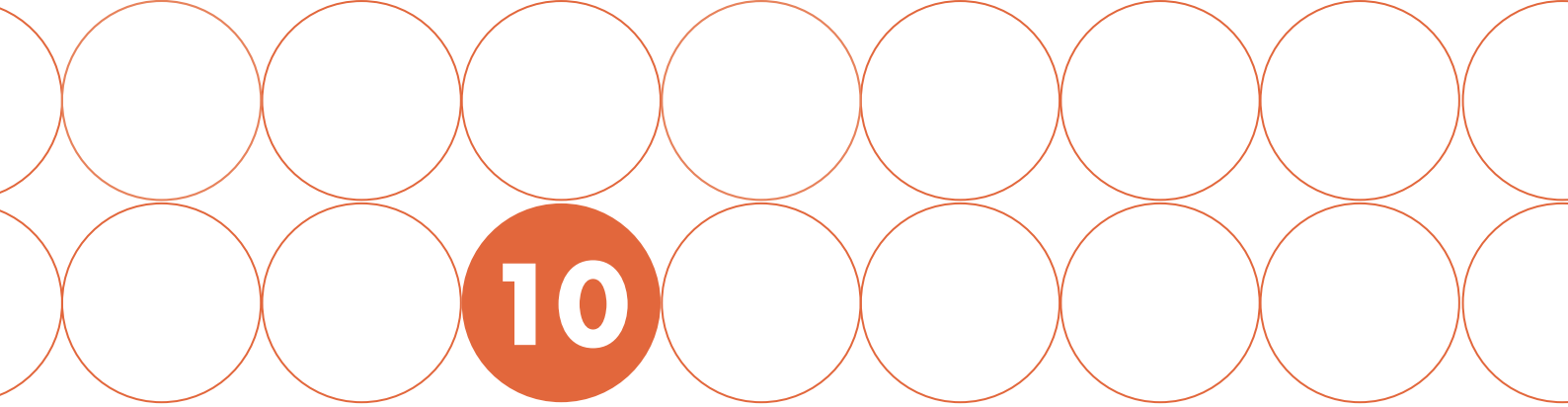




Chapter 10

Depression and Substance Use Disorders

Kirk J. Brower, M.D.

EPIDEMIOLOGY

Prevalence of Co-occurring Depressive and Substance Use Disorders

Several epidemiological studies of the general population in the United States have analysed the co-occurrence of depressive disorders and substance use disorders (SUDS). Among them, the National Epidemiological Survey on Alcohol and Related Conditions (NESARC) examined the co-occurrence of disorders in the previous 12 months among 43,093 individuals and found that approximately 20% of individuals with diagnoses of either major depressive disorder or dysthymic disorder also had a substance use disorder (Grant et al. 2004). Stated as odds ratios, individuals with major depressive disorder were nearly four times as likely to have alcohol dependence and nine times as likely to have other drug dependence compared with individuals without major depression (Grant et al. 2004). Conversely, individuals with alcohol dependence or other drug dependence had approximately 2 or 4 times the odds, respectively, of having major depression in the previous 12 months compared with those without alcohol or drug dependence (Hasin et al. 2005). In summary, having a substance use disorder increases the likelihood of having a concurrent depressive disorder and vice versa. Moreover, the mechanisms by which depressive disorders and SUDS are related may have a neurobiological basis, which preclinical research may help to delineate (Paterson and Markou 2007).

Course

Among clinical populations, alcohol use disorders predict greater severity of, and poorer outcomes for, mood disorders. Among psychiatric inpatients and outpatients with major depression, for example, having an alcohol use disorder increased the odds for suicidal ideation and attempts by factors of 2.2 and 6.3, respectively (Sokero et al. 2003). Sullivan et al. (2005) reviewed four other studies that showed an increase in suicidal symptoms or acts in depressed patients with a current or lifetime history of an alcohol, including two studies that showed statistically significant increases. Sullivan et al. (2005) also reviewed six studies that had investigated the effects of alcohol problems on the course of depression, two of which found that alcohol problems significantly worsened the course of depression (Cook et al. 1991; Mueller et al. 1994). The study by Mueller et al. (1994) followed 588 patients with major depression for 10 years and found that remissions from depression were less likely among patients with current alcohol dependence than among patients with either no history or a past history of alcohol dependence. Because depressed patients with and without a history of alcohol dependence did not differ in the course of their depressive illness, whereas those with a current alcohol dependence showed the worst course, this study suggests that successfully treating alcohol dependence should improve the prognosis for major depression.

There is general consensus that depression increases the risk for relapse in patients with SUDS (Curran et al. 2007; Landheim et al. 2006; Poling et al. 2007), including adolescent patients (Subramaniam et al. 2007). With respect to alcohol dependence, however, there are some studies for which drinking outcomes did not differ as a function of depression and other studies in which depression predicted *better* drinking outcomes in men (Kranzler et al. 1996b), women (Rounsaville et al. 1987), or both (Charney et al. 1998). Palfai et al. (2007) found that men with depression and alcohol-dependence had worse drinking outcomes than those without depression, whereas depression did not affect drinking outcomes in alcohol-dependent women. Hasin et al. (2002) argued that these inconsistencies between studies might be explained by different ways of classifying depression.

It is common to differentiate between substance-induced depression and independent major depression (Nunes et al. 2006). The usual assumption is that substance-induced depression clears within a few weeks of initiating abstinence from substances, whereas independent major depression has a longer and more severe course. Although this may be true, the course of substance-induced depression is not necessarily benign (Rounsaville 2004). Among 2,945 alcoholics, for example, rates of suicide attempts were significantly higher among those with

independent major depression (30.3%) compared with those with substance-induced depression (24.8%), but both rates are high and should raise clinical concerns (Schuckit et al. 1997). Likewise, in a smaller sample of 371 individuals with alcohol-dependence, the number of suicide attempts was significantly lower among those with substance-induced (mean=2.4) versus independent major depression (mean=4.6), but the two groups were equivalent in terms of their intention to die and likelihood of hospitalisation after the most serious attempt (Preuss et al. 2002).

Furthermore, Hasin et al. (2002) reported that substance-induced depression can interfere with achieving a stable remission. The authors studied 250 inpatients with cocaine, heroin, and/or alcohol dependence. Each patient received two classifications. First, they were classified according to whether their first lifetime episode of major depression (MD) preceded their substance use disorder or not, corresponding to the usual primary/secondary depression distinction. Second, patients were distinguished according to the current episode of MD that brought them into treatment. If the current MD episode started 2 or more weeks before using substances, or if it persisted 4 or more weeks after stopping substance use, then patients were classified as having a current episode of independent MD. Otherwise, their current MD episode was classified as substance-induced. Two outcomes were also measured for each patient. One outcome was achieving a 26-week remission from dependence during 18 months of follow-up (yes/no). The other outcome was relapsing to substance use after achieving a remission. Using the first classification, patients with primary MD disorder (first episode preceded diagnosis of substance dependence) were less likely than those with secondary depression to achieve remission. Using the second classification, patients with a current episode of substance-induced depression were also less likely to achieve a stable remission, whereas those with a current episode of independent major depression were three times more likely to relapse after achieving a stable remission than those with substance-induced depression. Thus, the course of the substance use disorder depended both on which lifetime disorder occurred first (major depression vs. substance dependence) *and* whether or not the current depressive episode was substance-induced or independent.

DIFFERENTIAL DIAGNOSIS AND SUBTYPES OF DEPRESSION

For patients with SUDS and depressive symptoms, the differential diagnosis for depression includes acute intoxication or withdrawal, substance-induced depression, adjustment disorder with depressed mood (due to multiple psychosocial consequences of use and stressors), major depression (unipolar versus bipolar), minor depression (dysthymia versus cyclothymia), depression due to a general medical condition, and complicated grief (Zuckoff et al. 2006). When a single best diagnosis is unclear, then a diagnosis of depression not other specified (NOS) can be made until additional history, examination, or longitudinal monitoring can clarify the diagnosis.

To complicate matters further, patients with comorbid SUDS and depression may also have other co-occurring disorders such as psychotic disorders, anxiety disorders, eating disorders, sleep disorders, attention-deficit/hyperactivity disorder, and personality disorders that can contribute to clinical manifestations or worsen treatment outcomes (Nunes et al. 2006). A discussion of these disorders is beyond the scope of this article.

Clinicians are often confronted with patients who simultaneously use substances and manifest depressive symptoms, and whose histories may initially be either unclear or unreliable. At the initial visit, many patients may appear symptomatically similar, yet be diagnostically different, with special implications for treatment. Differentiating substance-induced depression from independent major depression can be difficult but this distinction is important for treatment planning. When viewed prospectively, substance-induced depression typically remits within 4 weeks of successful abstinence-based treatment for addiction and does not require treatment with antidepressants, whereas untreated independent major depression typically persists despite early remission of SUDS and may require antidepressant treatment. Thus, monitoring the course of depressive symptoms after the patient achieves abstinence is preferred whenever possible. The optimal time for monitoring depressive symptoms prior to initiating antidepressant treatment, however, is subject to controversy. Although four

or more weeks is often recommended (American Psychiatric Association 2007), some patients may relapse before that time if their depressive symptoms interfere with treatment engagement and adherence. Moreover, other patients may not survive for 4 weeks, because the risk for suicide can increase if relapse to substance use occurs. Therefore, the optimal period for monitoring depressive symptoms while waiting to start antidepressant therapy should be made on an individual case-by-case basis. Nevertheless, the longer the period of abstinence, the more useful it is for diagnostic purposes.

If waiting for 4 or more weeks to monitor the course of depressive symptoms is not feasible, additional approaches to differential diagnosis may be employed. These include evaluation of the patient's personal history, his or her family history, and the patient's symptoms for congruence with substance-induced disorders. In evaluating the patient's history, the longitudinal course can be retrospectively evaluated using a timeline approach (Schuckit et al. 1997). The timeline begins with sequencing the onset of each disorder, which can result in three possibilities: 1) the depressive disorder preceded the onset of the substance use disorder, 2) the substance use disorder preceded the onset of the depressive disorder, or 3) both disorders had their onset concurrently or too close in time to prevent any conclusion about which came first ("the so-called chicken and egg paradox"). The first possibility suggests that the depressive disorder occurred independently of the substance use disorder; the second possibility suggests that the depression may be substance-induced; and the third possibility does not help to resolve diagnostic ambiguity.

Patients are also asked to recall periods in their lives when they did not use any substances to determine if any depressive episodes either started or persisted during earlier periods of prolonged abstinence. The new onset of a depressive episode for 2 or more weeks prior to using substances, or the persistence of a depressive episode during 1 or more months of abstinence, suggests that the depression occurred independently of the substance use disorder. Conversely, remission of depressive symptoms during periods of abstinence lasting at least 1 month is consistent with substance-induced depression. Even so, there are limitations to using past history to predict future course. A history of an independent major depressive episode, for example, does not preclude the possibility that the patient's current episode may be substance-induced and vice versa. Individual patients can have both substance-induced and independent major depressive episodes over the course of their lifetime.

Diagnostic congruency refers to the match or overlap between *expected* substance-induced symptoms and *observed* symptoms. For example, manic symptoms that occur during episodes of cocaine intoxication and depressive symptoms that occur during episodes of cocaine withdrawal are expected and congruent with substance-induced mood swings. Alternatively, a report of lots of energy and grandiose ideas without the need for sleep for several days despite drinking large amounts of alcohol (a CNS depressant) is unexpected and incongruent with substance-induced mania, but consistent with independent mania. According to the *Diagnostic and Statistical Manual of Mental Disorders, 4th Edition, Text Revision* (DSM-IV-TR), the following classes of substances are capable of inducing mood disorders: alcohol, amphetamines, cocaine, hallucinogens, inhalants, opioids, phencyclidine, and sedatives/hypnotics/anxiolytics (American Psychiatric Association 2000, p. 193). To this list can be added anabolic steroids (Pope and Brower 2005). Interestingly, neither nicotine nor cannabis has been recognised by DSM-IV as having the potential to induce mood disorders, although these can be observed clinically.

Finally, a clear family history of one disorder or the other may help to determine if the depression is substance-induced or independent. Alcohol-dependent individuals with independent major depression are significantly more likely than those with alcohol-induced depression to have a first-degree relative with independent major depression (Schuckit et al. 1997). Therefore, establishing a diagnosis of major depression in a first-degree family member without a substance use disorder may increase the likelihood that the substance-using patient is also vulnerable to independent major depressive episodes. Of course, family history is not easily established in some cases, and in other cases (such as adoption) information about biological relatives may be missing altogether.

Many patients will report or have the experience of using substances to alleviate or distract themselves from depressive symptoms. Self-medication of depressive symptoms is a readily understandable clinical phenomenon. Using a self-medication perspective, one might even conceptualise some SUDS as being depression-induced. Nevertheless, a diagnostic category of depression-induced SUDS is not included in the DSM-IV-TR classification.

TREATMENT

When patients are diagnosed with independent depression and a substance use disorder, then treating both disorders in an integrated manner is indicated (American Psychiatric Association 2007b). In general, treatments for depression in the absence of a substance use disorder are also effective in depressed patients with a substance use disorder (Tiet and Mausbach 2007). Similarly, treatments for SUDS in the absence of depression are also effective in depressed patients with a substance use disorder. Nevertheless, there are special considerations when both disorders are present which are discussed in the following section.

Treatment Models

Three general models for treating patients with co-occurring disorders have been described. In the sequential model, one disorder (e.g., substance dependence) is treated first, followed by treatment of the other disorder (e.g., depression). This model may be appropriate for substance-induced depression. In the parallel model, both disorders are treated simultaneously with each disorder treated by a different clinical team. This model has been criticised for the potential lack of communication between teams, who may also adhere to different treatment approaches and give contradictory instructions to patients. In the integrated model, both disorders are treated simultaneously by one clinical team with dual expertise in SUDS and depression (Brunette and Mueser 2006).

Ideally, all treatment programs would have the expertise and resources for integrating specialised addiction treatment and mental health treatment for patients with co-occurring disorders. In reality, many programs do not have this capability. Sequential and parallel models of treatment are just as likely to occur, depending on where the patient presents for treatment. Although there is a general consensus that integrated models for treating co-occurring disorders are preferable (American Psychiatric Association 2007), a recent review of the literature concluded that more evidence was needed (Tiet and Mausbach 2007).

Treatment Sites and Levels of Care

Patients with co-occurring disorders may enter the health care system through a number of different "doors", such as hospital emergency departments, inpatient units, primary care and medical speciality outpatient clinics, mental health treatment clinics, and specialised addiction treatment programs. All patients entering mental health treatment clinics should be screened for SUDS, and all patients entering addiction treatment programs should be screened for mood disorders (American Psychiatric Association 2007). If the patient has entered the health care system at a site that cannot provide integrated care, then referral may be indicated depending on the severity of each disorder. Guidelines are available for determining the optimal level of care for treatment of SUDS that account for psychiatric disorders and complications (American Psychiatric Association 2007; American Society of Addiction Medicine 2001), but access is limited world-wide by stigma, shame, lack of insight and motivation, and—at least in the United States—inability to pay. More intensive levels of care facilitate safety in terms of short-term risk for relapse and suicide. They also allow for prospective monitoring of the patient's depression symptoms in a safe environment to clarify whether they are substance-induced or independent.

Treatment Goals

To the usual goals of treatment (abstinence, symptom reduction, and improved psychosocial functioning) is added one other goal unique to co-occurring disorders: to minimise the negative impact of one disorder on the other. This latter goal applies particularly to cases in which there is diagnostic uncertainty about whether a patient's depression is substance-induced or independent. If depressive symptoms interfere with a patient's participation in addiction treatment, or increase the patient's risk for suicide or addiction relapse, then the threshold to treat depression as an independent disorder is lowered to avoid a negative impact even if the diagnostic subtype of depression remains unclear (Table 10.1).

The Threshold Approach to Treatment Timing

Most psychiatrists prefer to wait and see if depressive symptoms will resolve after 4 or more weeks of abstinence before starting an antidepressant medication (Nunes and Levin 2006). Advantages of waiting are that it allows for 1) an accurate assessment of depressive symptoms when the patient is "clean", 2) substance-induced depressive and protracted withdrawal symptoms to clear, and 3) the focus of initial treatment to target addiction. It also avoids sending a message to the patient that there is "a pill for every ill", and encourages patients to seek non-chemical solutions to their problems. Disadvantages of waiting occur when the depressive symptoms interfere with the patient engaging and participating in addiction treatment, or when depressive symptoms increase the patient's risk of suicide. Because it can take several weeks and even months to find the right dose of the right antidepressant for a particular patient, some psychiatrists argue that the patient's best interest is served by treating depressive symptoms early, especially when depressive symptoms are life-threatening or are having a negative impact on addiction treatment. To balance concerns about premature versus "too-late" treatment with antidepressants, clinical guidelines emphasise factors that either increase or decrease the threshold to start antidepressant treatment, as summarised in Table 10.1 and Figure 10.1. In summary, treatment cannot always wait until diagnostic clarity is achieved, because waiting may increase the risk of suicidality or relapse to substance use. Therefore, arbitrary periods of required abstinence cannot be recommended across all cases. Nevertheless, treatment of actively drinking alcohol-dependent patients is unlikely to be effective (Baigent 2005).

Pharmacotherapy

Several reviews and meta-analyses of pharmacotherapy for co-occurring SUDS and depression have recently been published (Berglund et al. 2003; Goldstein et al. 2006; Lingford-Hughes et al. 2004: Nunes and Levin 2004; Torrens et al. 2005). Nunes and Levin (2004) published a meta-analysis of 14 double-blind, placebo-controlled trials involving 848 patients involving three classes of antidepressants (5 tricyclic antidepressants [TCAs], 7 selective serotonin reuptake inhibitor [SSRIs], 2 other antidepressants) and dependence on three different substances (8 alcohol, 2 cocaine, and 4 opioids). In these studies antidepressant medication had a limited impact on alcohol and drug use, but produced significant response in depression (52.1% vs. 38.1 with placebo). Similarly, in adolescents with major depression and SUDS, Riggs et al. (2007) found that fluoxetine significantly reduced levels of depression compared with placebo, but did not confer an advantage in reducing substance use.

In general, the same medications for the same duration of time that are used to treat disorders when they occur alone are also used to treat them when they co-occur together. Nevertheless, several caveats are warranted when applying this approach (Figure 10.1). Medications with abuse potential and/or the potential for adverse interactions with the patient's drug of choice should be avoided or used very cautiously, as should medication with a high potential for overdose, especially when mixed with alcohol and other drugs of abuse. For these reasons, sedative-hypnotics and psychomotor stimulants are not first-choice drugs when medicating depressed patients with SUDS for anxiety, insomnia, or comorbid attention-deficit/hyperactivity disorder (ADHD).

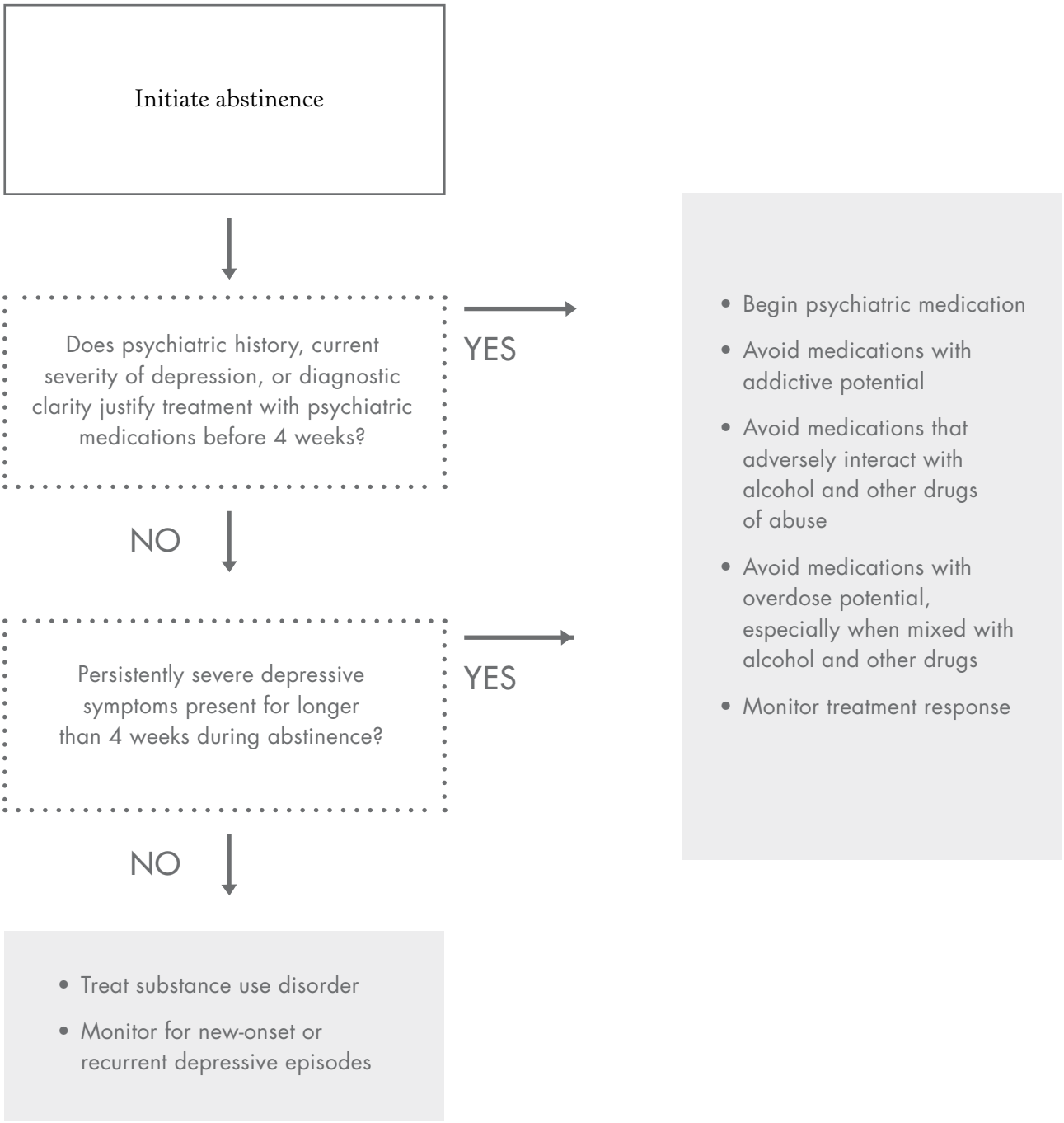
TABLE 10.1

Factors that alter the threshold for treating depression early in the course of addiction treatment

Decrease threshold for early treatment Diagnostic clarity	Increase threshold for early treatment Diagnostic ambiguity
Symptom severity interferes with participation in addiction treatment, increases risk for relapse, or increases risk for suicide.	Symptom severity does not interfere with addiction treatment, increase risk for relapse, or increase risk for suicide.
Retrospective history clearly indicates that the onset of depressive disorder preceded onset of the substance use disorder.	Retrospective history clearly indicates that the onset of the substance use disorder preceded onset of the depressive disorder.
Retrospective history clearly indicates that depressive disorder persisted during at least one prior episode of abstinence lasting for 4 or more weeks.	Retrospective history clearly indicates that depressive symptoms remitted within 4 weeks of prior abstinent episodes.
First-degree family history of substance-independent major depressive episode.	No family history of substance-independent major depressive episode.
Outpatient care where depression combined with chaotic social system or insufficient coping skills increases suicide/relapse risk.	Intensive levels of care where decompensation from depression can be quickly observed and treated without risk of relapse or suicide.

FIGURE 10.1

When to initiate antidepressant treatment in a patient with dual diagnoses



Non-addictive medications or psychosocial treatments for anxiety, insomnia (Arnedt et al. 2007), or ADHD should be considered first. If benzodiazepines are to be used, then several safeguards are recommended. For patients with alcohol dependence, benzodiazepines can be made contingent on taking disulfiram (unless medically contraindicated), in order to decrease the overdose risk of combining benzodiazepines with alcohol ingestion. In all cases, patients and prescribing clinicians should agree in writing about selecting a sole prescribing clinician, bringing pills for a count at every visit, specifying rules for lost pills, giving consent for the clinician to speak with a significant other who can provide corroborative history, and obtaining urine drug screens to rule out use of non-prescribed drugs of abuse. Prescribing clinicians should also rule out a history of overdose as a method for suicide attempts and provide time-limited prescriptions without refills. Substance-specific pharmacotherapy trials are reviewed below.

Alcohol dependence

Randomized controlled trials of antidepressants in patients with alcohol-dependence and co-existing major depression have produced mixed results. In general, antidepressants improved mood in most but not all studies, but only modest effects on drinking outcomes were observed across most studies (Lingford-Hughes et al. 2004; Pettinati 2004; Torrens et al. 2005). For example, TCAs reduced depressive symptoms in alcohol-dependent outpatients with primary major depression in one study (McGrath et al. 1996) and secondary major depression in another (Mason et al. 1996), but reduction in drinking was modest and observed mostly among patients whose depression improved. Fluoxetine had a positive effect on both depression and drinking outcomes in a study by Cornelius et al. (1997, 2000), which selected for psychiatric inpatients who were admitted in part for suicidal thinking or behaviours. In a study of 82 outpatients with comorbid depression, sertraline reduced drinking more than placebo in both men and women, but only women showed an antidepressant effect (Moak et al. 2003). In contrast, Pettinati et al. (2001) found that sertraline reduced drinking significantly more than placebo in outpatients *without* a lifetime history of major depression, but did no better than placebo for outpatients *with* a lifetime history of major depression. Finally, the largest trial of sertraline to date in this area (N = 328) found no benefit over placebo in reducing either drinking or depressive symptoms, due in part to a large placebo response (Kranzler et al. 2006). Nefazodone has also been studied with mixed results in patients with alcohol dependence and co-occurring major depression. It significantly reduced depression but not drinking in one placebo-controlled trial (Roy-Byrne et al. 2000), while it reduced drinking but not depression in another (Hernandez-Avila et al. 2004). In Europe and other countries, the antidepressant tianeptine has been used successfully to treat depression in patients with alcohol-dependence (Habrat and Zaloga 2006). Although it is unlikely to improve drinking outcomes in nondepressed patients (Favre et al. 1997), it is not metabolised in the liver, which is an advantage for use in depressed alcohol-dependent patients with liver impairment.

Other studies show that the typology of alcoholism may affect response to SSRI antidepressants. Kranzler et al. (1996a) reported that two subtypes of alcohol dependence were found to respond differentially to fluoxetine 60 mg/day. The type A subtype (onset of dependence after reaching 25 years of age, limited psychopathology, few drinking-related problems, and few childhood risk factors) drank the same amount as the placebo group, whereas the Type B subtype (early-onset occurring before age 25, more severe psychopathology, antisocial and impulsive tendencies) drank more than the placebo group. Pettinatti and colleagues (2000) published findings that were consistent with these for type B alcoholics treated with sertraline 200 mg/day. Cornelius et al. (1998) found that comorbid cocaine abuse significantly worsened outcomes for depressed patients with alcohol dependence who were treated with fluoxetine. Therefore, SSRI antidepressants should be used cautiously in patients with type B alcohol dependence and in individuals with alcohol dependence who also abuse cocaine.

Depression is not a contraindication for treating alcohol dependence with medications such as naltrexone (Maxwell and Schinderman 2000; Oslin 2005; Salloum et al. 1998), acamprosate (Morley et al. 2006), or disulfiram in doses of 250 mg/day (Petrakis et al. 2007), although placebo-controlled trials of these agents have found mixed effects on drinking outcomes. For example, one study that compared naltrexone, acamprosate, and placebo in alcohol-dependent patients with "clinically relevant" levels of depression found no differences in drinking outcomes (Morley et al. 2006). In another study, naltrexone was found to be superior to acamprosate and placebo in increasing abstinence rates in patients with high levels of baseline depression (Kiefer et al. 2005). In a third study, disulfiram significantly reduced craving compared with naltrexone, but this did not translate into decreased use of alcohol (Petrakis et al. 2007). Before prescribing disulfiram, however, alcohol-dependent patients with both depression and impulsivity need to be evaluated for potential self-harm that could result from drinking in combination with disulfiram. Moreover, disulfiram can prolong the half-life of benzodiazepines and TCAs and can interact with monoamine oxidase inhibitors to cause toxic psychosis. If TCAs are used, it is recommended that the clinician choose an agent for which meaningful serum concentrations are available, because alcohol-dependent patients may metabolise TCAs more quickly in early stages of their recovery (Mason 1996). Finally, the product labelling of extended release intramuscular naltrexone indicates that adverse events involving suicidal thoughts or behaviours occurred in 1% of patients treated with naltrexone versus none of the patients treated with placebo (Swainston Harrison et al. 2006). Most psychiatrists do not consider naltrexone to be "depressogenic" (Miotto et al. 2002; Petrakis et al. 2007; Salloum et al. 1998), despite a single case report to the contrary (Schurks et al. 2005). Nevertheless, patients with alcohol dependence and co-occurring major depression are well known to have an increased risk for suicide, and to require close monitoring to identify the need for possible intervention (Cornelius et al. 2004).

Nicotine dependence

Smoking cessation has been associated with the onset or exacerbation of depression, and depressive symptoms are associated with poor smoking cessation outcomes (Brown et al. 2007). On the other hand, depression was not a predictor of smoking cessation outcomes in a population maintained on methadone who were treated with a combination of nicotine replacement and a brief behavioural intervention (Stein et al. 2007), nor did depressive symptoms predict abstinence from cigarettes in patients with alcohol-dependence (Kodl et al. 2008). Trials of antidepressants in the treatment of treat nicotine dependence have demonstrate that bupropion and nortriptyline are efficacious in patients with and without a history of major depression (Brown et al. 2007; Torrens et al. 2005). Combining bupropion with nicotine replacement therapy is another promising strategy (Ait-Daoud et al. 2006). An alternative approach is to use nicotine replacement therapy in combination with antidepressants such as SSRIs, which by themselves are not thought to have efficacy for smoking cessation. Studies of varenicline in depressed smokers are needed.

Cannabis dependence

Pharmacotherapy of marijuana dependence with or without comorbid depression is understudied. Cornelius et al. (1999) reported that fluoxetine was more effective than placebo in reducing marijuana use among depressed patients with alcoholic dependence.

Cocaine dependence

Two recent reviews of the literature reached opposite conclusions about the efficacy of antidepressants in depressed patients with cocaine dependence. Based on the findings of a meta-analysis, Torrens et al. (2005) concluded that antidepressants failed to significantly decrease depressive symptoms in patients with both disorders. Rounsaville (2004) concluded that the preponderance of evidence supported the use of antidepressants to treat major depression in patients with cocaine-dependence, although mixed results in the evidence were also acknowledged. Rounsaville (2004) also suggested

that the more stimulating antidepressants, such as bupropion and desipramine, might be more effective than SSRIs for treating stimulant-induced depression. The toxicity and overdose potential of bupropion and desipramine, as well as their interactions with cocaine, require clinical consideration before their use.

Opioid dependence

Antidepressant treatment of depressed patients with opioid-dependence is best studied in methadone-maintained patients, but the evidence is mixed (American Psychiatric Association 2007, p. 37), so that data are not available on which to base recommendations for most patients (Nunes et al, 2004; Torrens et al, 2005). Because of the role of the opioid system in the experience of pleasure, the question arises as to whether naltrexone increases anhedonia and depression. Although this occur in individual cases (Schurks et al. 2005), this did not occur in a randomized trial of non-depressed, methadone-maintained patients with opioid dependence (Dean et al. 2006), during which no difference in depressive symptoms was found between those randomly assigned to continue methadone versus switching to naltrexone. Naltrexone is not necessarily contraindicated in depressed patients (see above), although heroin users have been reported to be more vulnerable to overdosing as a result of reduced tolerance or opioid receptor sensitisation upon stopping naltrexone (Ritter 2002). Buprenorphine and methadone have been associated with improved mood in patients with opioid-dependence (Dean et al. 2004; Nunes et al. 2004). In a retrospective study, buprenorphine reduced opioid use just as well in depressed as nondepressed patients with heroin-dependence (Gerra et al. 2006). Because it is a partial agonist at mu opioid receptors, buprenorphine has the advantage of having a lower potential for both abuse and overdose than methodone. Both agents are metabolised in the liver by cytochrome (CYP) enzyme 3A4, so that carbamazepine and barbiturates can decrease the levels of these agents, whereas fluoxetine, fluvoxamine, and nefazodone can increase them.

Psychosocial Therapy

Psychosocial/behavioural therapies are always indicated to treat SUDS because currently available pharmacotherapies have limited efficacy when used alone and are therefore only used adjunctively. Evidence-based psychotherapies for SUDS include cognitive-behavioural therapy (CBT), twelve-step facilitation therapy (TSF), motivational enhancement therapy (MET), contingency management (CM), and behavioural couples therapy (American Psychiatric Association 2007; Conroy et al. 2008; Dutra et al. 2008). Evidence-based psychotherapies for major depressive disorder (MDD) include CBT, interpersonal psychotherapy, group psychoeducation, and problem-solving treatment (American Psychiatric Association 2000; Fochtmann and Gelenberg 2005). When considering psychosocial therapy for co-occurring disorders, a number of important questions arise. First, are psychotherapies for addiction effective among patients with co-occurring major depression? Second, are psychotherapies for depression effective among patients with SUDS? Third, are there cross-diagnostic benefits? For example, do psychotherapies for addiction decrease depressive symptoms, and do psychotherapies for depression decrease substance use among addicted patients? Fourth, are integrated psychotherapies, which are designed to treat both depression and SUDS, more effective than psychotherapies that focus on a single diagnosis? In general, these questions remain unanswered and warrant further clinical trials (Carroll 2004). Therefore, the studies described below do not represent a comprehensive review of psychotherapy trials for SUDS and co-occurring depression. Rather, they are presented with the more modest goal of illustrating the types of questions that researchers are beginning to address as well as the complexity of issues facing clinicians in this area.

Regarding the first question, at least three recent studies suggest that addiction-focused psychotherapy is effective in improving substance use outcomes in depressed patients with co-occurring SUDS. Gonzales et al. (2003) studied cocaine-abusing outpatients taking buprenorphine for opioid dependence, and found that CM was superior to non-contingency management in terms of drug-free urine tests among patients with a lifetime history of major depressive disorder, but that no differences between groups were found for reduction in depression. Brown et al. (2006) conducted a 26-week randomized trial comparing TSF and integrated CBT, provided in a twice weekly group format. Subjects were a diagnostically mixed group of patients with alcohol, marijuana, and/or stimulant dependence comorbid with major depression. Integrated CBT was designed to address both substance abuse and depression, whereas TSF was focused on addiction. Patients showed significant improvement in both percentage of days abstinent and depression scores, but without significant differences between treatment groups and with levels of depression remaining elevated. In other words, the addiction-focused treatment, TSF, improved substance use outcomes in depressed patients. In the third study, Bellack et al. (2006) conducted a randomly controlled trial in a mixed group of patients with severe and persistent mental illness, 56% of whom had major affective disorders and either cocaine, heroin, or cannabis dependence. The study reported superior outcomes in terms of clean urine test results, attendance, and remaining in treatment for patients receiving behavioural treatment for substance abuse versus supportive group therapy. The behavioral therapy used in this study was a 6-month multimodal treatment consisting of small-group therapy, individual motivational interviewing sessions, social skills training, relapse prevention, and CM that provided monetary rewards for clean urine tests. Depression outcomes were not reported. Thus, the finding that addiction-focused treatment can improve substance use outcomes in depressed patients was found across three different addiction therapies (CM, TSF, broad-spectrum behavioral therapy) and across several different substances (alcohol, opioids, stimulants, cannabis).

With regard to the second question, there is some support for the conclusion that psychotherapies for depression reduce depressive symptoms in patients with co-occurring SUDS. Carpenter et al. (2006) conducted an uncontrolled study of a 16-week regimen of behavioural therapy for depression in 29 methadone-maintained patients with opioid-dependence and found a reduction in depression but not in cocaine or opioid use. Thus, behavioural therapy for depression reduced depressive symptom but did not show a cross-diagnostic effect in reducing substance use.

Two other studies are pertinent to the third question about cross-diagnostic treatment effects. The study cited above by Bellack et al. (2006) found that TSF therapy for addiction worked to reduce depression. A negative study by Brown et al. (2007) did not find that adding CBT for depression to standard CBT for smoking cessation improved outcomes for smoking cessation in a 12-week randomized trial. However, only 21% of 524 subjects had a lifetime history of major depression, and lack of subtyping for major depression may have obscured a positive result, as suggested by Hasin et al. (2002) (see above).

With regard to the fourth question regarding integrated treatment, the study by Brown et al. (2006) discussed above showed no advantage for integrated CBT over TSF in terms of either substance use or depression outcomes. Similarly, there is a general consensus that combining medication and behavioral therapy in treatment for smoking cessation is more effective than either alone, but it is still unclear whether there is a specific role for providing mood management skills in training for depressed smokers (Ait-Daoud et al. 2006).

Another question is whether certain therapeutic styles are associated with better response. For example, Karno and Longabaugh (2007) reported that patients with alcohol-dependence and high levels of depression on the Beck Depression Inventory had better drinking outcomes when matched with therapists who guided patients away from emotionally charged topics. Thus, the qualities of the patient-therapist interaction may affect outcomes, independent of the type of psychotherapy being provided.

CONCLUSIONS

The co-occurrence of depressive disorders and SUDS is common in both general and clinical populations. It is generally accepted that co-occurring depressive disorders and SUDS are associated with poorer outcomes than either disorder alone. However, there are enough exceptions to this general statement to justify approaching patients who have co-occurring disorders with the same therapeutic optimism as one would for patients having only one disorder or the other.

Patients with SUDS can be depressed for reasons related to 1) the substance itself (acute intoxication, withdrawal, substance-induced depression, and adjustment disorder to multiple adverse consequences and losses from use) and/or 2) the co-occurrence of independent mood disorders (major depressive episodes associated with unipolar and bipolar disorders, and minor depression associated dysthymic and cyclothymic disorders). Other mental disorders, including personality disorders, as well as medical disorders may further complicate the clinical picture. Despite all these diagnostic possibilities, psychiatrists are usually most concerned with distinguishing independent major depression from substance-induced depression. If either a retrospective timeline history of abstinent periods or prospective monitoring with ongoing abstinence suggests at least one episode of independent major depression, then that diagnosis will help guide the treatment plan. Symptom incongruence and family history may also help to distinguish independent major depression from substance-induced depression. The longer the period of abstinence, the more useful it is for differential diagnosis. Nevertheless, treatment cannot be delayed until diagnostic clarity is achieved, because waiting may increase the risk for suicide or relapse to substance use.

Pharmacotherapy trials indicate that antidepressants have a greater effect on depressive symptoms than substance use outcomes (Nunes and Levin 2004), with the exception of nicotine dependence, for which smoking cessation is enhanced and depression is reduced (Torrens et al. 2005). Among patients with alcohol dependence, subtypes of alcoholism may affect the response to antidepressants. Psychosocial therapies are always indicated for SUDS, but further clinical trials are needed to determine if the cross-diagnostic treatment effects of psychotherapies focused primarily on addiction or depression are comparable to the benefits of integrated psychosocial therapies.

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