Depression and Anxiety

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I. INTRODUCTION

Depressive disorders encompass a wide spectrum of conditions. The American Psychiatric Association's Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition (DSM-IV) includes major depression (both single episode and recurrent), dysthymic disorder, adjustment disorder with depressed mood, mood disorder due to a general medical condition, substance-induced mood disorder, and depressive disorder not otherwise specified in its classification. Anxiety is present in about 80% of depressed patients.

Depression is one of the most common disorders seen by primary care practitioners. The lifetime prevalence of a major depressive disorder is 7% to 12% for men and 20% to 25% for women. Between 5% and 10% of primary care patients will meet the criteria for major depression at any given time, although fewer than half will receive treatment for their disorder. Among medically ill hospitalized patients, an estimated 20% to 33% will meet the criteria for major depression.

The cost of depressive disorders is enormous, both financially and otherwise. Estimates range up to $40 billion per year in the United States for expenses related to treatment, time lost from work, and other measures of lost productivity. However, the cost of depressive disorders in terms of human suffering and disability is less easily quantified. Mortality among depressed patients is significantly increased through an exacerbation of medical illness, accidents, and suicide.

Society's view of mental illness is often based more on misperception and fear than on the knowledge and awareness that it represents a true disease process. Consequently, concerned relatives and friends frequently regard depression not as the illness it is, but...
rather as a shortcoming on the part of the individual or as something the patient should be capable of “just snapping out of.” Indeed, many patients view their own depression as a personal failure and fear that the treatment will be worse than the disease. Too often, physicians avoid considering depression in their differential diagnosis of patients, especially patients who present with vague somatic symptoms. Denial, both conscious and unconscious, is widespread when it comes to diagnosing and treating depression. Yet only by overcoming this denial and embarking on a public campaign of psychoeducation will physicians be able to help the millions of undiagnosed sufferers of depression.

II. CASE PRESENTATION

A 38-year-old Hispanic man is seen for evaluation at a university-based family practice clinic. The patient tells the physician that he was diagnosed as being HIV positive 12 years earlier and that he contracted the virus through shared needles while dependent on heroin. His initial reaction upon learning of his diagnosis was to feel desperate and to seriously contemplate suicide. However, those feelings subsided as he gradually began to accept his diagnosis.

Beginning approximately 3 years ago, the patient began feeling increasingly sad and depressed, a feeling that persisted nearly every day. Although his medical condition has been remarkably stable for some time, he has been thinking more and more that his time is quickly running out. Other symptoms he has experienced include severe anxiety, loss of interest in pleasurable activities, isolation from family and friends, and feelings of hopelessness, helplessness, and worthlessness. His energy level is low, and his sleep and appetite are poor. He reports that he has lost some weight but cannot say exactly how much. He denies any suicidal thoughts or psychotic features. He states that he has been totally clean from drugs for more than 6 years. He denies any past psychiatric history other than his prior drug use. When questioned as to why he never sought psychiatric help, he states that he feared being “brainwashed.”

III. DIAGNOSIS

- Do the patient’s symptoms meet the diagnostic criteria for major depression?
- What other diagnoses must be included in the differential diagnosis?

- What other diagnostic tools can be employed to support the diagnosis and to monitor the patient’s response to treatment?

CLINICAL PRESENTATION

The essential feature needed to make a diagnosis of major depression is the presence of a depressed mood or a marked loss of interest or pleasure lasting for a period of 2 weeks or longer and representing a change from a previous level of functioning. Additionally, patients must present with at least 5 of the 9 symptoms listed in the DSM-IV criteria for a major depressive episode in order to confirm the diagnosis (Table 1).

CHARACTERISTIC SYMPTOMS

Patients with major depression most commonly present with complaints of decreased or diminished energy (97% of patients). This frequently leads to an impaired ability to function adequately in school, work, or at home. Important tasks are neglected or are only partially completed. Decreased motivation prevents patients from undertaking new endeavors.

Anxiety, although not a criterion for major depression according to the DSM-IV, is another extremely common symptom (80% of patients). At its extreme, patients can appear restless or even severely agitated. Pacing and hand-wringing are common manifestations of anxiety. Psychomotor agitation or retardation is listed among the DSM-IV criteria for a major depressive episode.

Vegetative symptoms such as sleep and appetite changes are also extremely common manifestations of depression. Approximately 80% of patients complain of insomnia, which usually takes the form of early morning awakenings or terminal insomnia. Patients typically complain of tossing and turning in bed while ruminating about their problems. Poor appetite is frequently associated with a 5% or greater loss in body weight without any conscious intent to lose weight. Occasionally, patients present with atypical features such as hypersomnia and increased appetite. Such patients commonly report a desire to “sleep away” or “eat away” their problems. Vegetative symptoms can also include decreased sexual activity and decreased interest in sex.

Cognitive dysfunction, which occurs in 67% to 84% of patients, can manifest itself as a diminished ability to think or concentrate. In older patients, this cognitive dysfunction can be so severe that 15% of depressed elderly patients can appear to be significantly demented. The term used to describe this phenomenon, pseudodementia, is gradually giving way to the more current term, the dementia syndrome of depression. However, patients with depression typically retain greater insight
Table 1. DSM-IV Diagnostic Criteria for a Major Depressive Episode

A. Five (or more) of the following symptoms have been present during the same 2-week period and represent a change from previous functioning; at least 1 of the symptoms is either (1) depressed mood or (2) loss of interest or pleasure. Note: Do not include symptoms that are clearly due to a general medical condition, or mood-incongruent delusions or hallucinations.

1. Depressed mood most of the day, nearly every day, as indicated by either subjective report (eg, feels sad or empty) or observation made by others (eg, appears tearful). Note: in children and adolescents, can be irritable mood.

2. Markedly diminished interest or pleasure in all, or almost all, activities most of the day, nearly every day (as indicated by either subjective account or observation made by others).

3. Significant weight loss when not dieting or weight gain (eg, a change of more than 5% of body weight in a month) or decrease or increase in appetite nearly every day. Note: in children, consider failure to make expected weight gains.

4. Insomnia or hypersomnia nearly every day.

5. Psychomotor agitation or retardation nearly every day (observable by others, not merely subjective feelings of restlessness or being slowed down).

6. Fatigue or loss of energy nearly every day.

7. Feelings of worthlessness or excessive or inappropriate guilt (which may be delusional) nearly every day (not merely self-reproach or guilt about being sick).

8. Diminished ability to think or concentrate or indecisiveness nearly every day (either by subjective account or as observed by others).

9. Recurrent thoughts of death (not just fear of dying), recurrent suicidal ideation without a specific plan, or a suicide attempt or a specific plan for committing suicide.

B. The symptoms do not meet criteria for a mixed episode.

C. The symptoms cause clinically significant distress or impairment in social, occupational, or other important areas of functioning.

D. The symptoms are not due to the direct physiological effects of a substance (eg, a drug of abuse, a medication) or a general medical condition (eg, hypothyroidism).

E. The symptoms are not better accounted for by bereavement; that is, after the loss of a loved one, the symptoms persist for longer than 2 months or are characterized by marked functional impairment, morbid preoccupation with worthlessness, suicidal ideation, psychotic symptoms, or psychomotor retardation.


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lasting 2 years or more. An episode of major depression is sometimes superimposed on a dysthymic disorder and is then termed a double depression. Dysthymia can present as a primary disorder or it may occur secondary to chronic medical problems or even other non-mood psychiatric disorders. The DSM-IV criteria for dysthymic disorder are presented in Table 2.

Seasonal Affective Disorder

A variation of depressive illness occurs in patients with seasonal affective disorder.10 These individuals typically experience the recurrence of their depressive illness in the late fall or winter months, when exposure to sunlight is limited. The prevalence ranges from 2% to 10%, with the greatest prevalence seen in those who live in latitudes furthest from the equator. Phototherapy is a treatment option for many of these patients.

Postpartum Depression

Major depressive episodes that begin within 6 months following delivery occur in approximately 10% to 15% of postpartum women. Postpartum depression must be distinguished from “postpartum blues,” which is a time-limited condition that develops within 2 to 3 days after delivery and lasts up to 2 weeks. Mood lability is a central feature of postpartum blues and occurs in approximately 50% to 75% of postpartum women. The development of psychotic features in postpartum depression is higher in women with a prior history of psychiatric illness.11

Depressive Equivalents

A major contributing factor in the underdiagnosis of depression is the variety of presentations. Children and geriatric patients in particular may be unable to articulate how they feel when describing their mood. Instead, they present with depressive equivalents, a variety of alternate symptoms and manifestations of their depression. Children frequently develop school-related problems such as school phobia, decline in academic performance, and truancy. Adolescents often start “acting out”—engaging in sexual promiscuity, substance use, and other antisocial behaviors. On the other hand, older patients commonly present with vague somatic complaints such as fatigue, headache, insomnia, chronic pain, and gastrointestinal problems. Extensive medical work-ups usually prove negative.12

ASSESSMENT TOOLS

A variety of easy-to-use self-reporting rating scales can be used as screening devices for depression. A commonly used tool is the Beck Depression Inventory,

<table>
<thead>
<tr>
<th>Table 2. DSM-IV Diagnostic Criteria for Dysthymic Disorder</th>
</tr>
</thead>
<tbody>
<tr>
<td>Depressed mood for most of the day, for more days than not, as indicated either by subjective account or observation by others, for at least 2 years. Note: In children and adolescents, mood can be irritable and duration must be at least 1 year.</td>
</tr>
<tr>
<td>B. Presence, while depressed, of 2 (or more) of the following:</td>
</tr>
<tr>
<td>(1) Poor appetite or overeating</td>
</tr>
<tr>
<td>(2) Insomnia or hypersomnia</td>
</tr>
<tr>
<td>(3) Low energy or fatigue</td>
</tr>
<tr>
<td>(4) Low self-esteem</td>
</tr>
<tr>
<td>(5) Poor concentration or difficulty making decisions</td>
</tr>
<tr>
<td>(6) Feelings of hopelessness</td>
</tr>
<tr>
<td>C. During the 2-year period (1 year for children or adolescents) of the disturbance, the person has never been without the symptoms in criteria A and B for more than 2 months at a time.</td>
</tr>
<tr>
<td>D. No major depressive episode has been present during the first 2 years of the disturbance (1 year for children and adolescents); ie, the disturbance is not better accounted for by chronic major depressive disorder or major depressive disorder in partial remission.</td>
</tr>
<tr>
<td>Note: There may have been a previous major depressive episode provided there was a full remission (no significant signs or symptoms for 2 months) before development of the dysthymic disorder. In addition, after the initial 2 years (1 year in children or adolescents) of dysthymic disorder, there may be superimposed episodes of major depressive disorder, in which case both diagnoses may be given when the criteria are met for a major depressive episode.</td>
</tr>
<tr>
<td>E. There has never been a manic episode, a mixed episode, or a hypomanic episode, and criteria have never been met for cyclothymic disorder.</td>
</tr>
<tr>
<td>F. The disturbance does not occur exclusively during the course of a chronic psychotic disorder, such as schizophrenia or delusional disorder.</td>
</tr>
<tr>
<td>G. The symptoms are not due to the direct physiologic effects of a substance (eg, a drug of abuse, a medication) or a general medical condition (eg, hypothyroidism).</td>
</tr>
<tr>
<td>H. The symptoms cause clinically significant distress or impairment in social, occupational, or other important areas of functioning.</td>
</tr>
<tr>
<td>Specify if:</td>
</tr>
<tr>
<td>Early onset: if onset is before age 21 years</td>
</tr>
<tr>
<td>Late onset: if onset is age 21 years or older</td>
</tr>
<tr>
<td>Specify (for most recent 2 years of dysthymic disorder):</td>
</tr>
<tr>
<td>With atypical features</td>
</tr>
</tbody>
</table>

a 21-item questionnaire that most patients can com-
plete in 5 minutes.\textsuperscript{13} Others include the General Health
Questionnaire, the Center for Epidemiological Studies
Depression Scale, and the Zung Self-Reporting Depres-
sion Scale.\textsuperscript{14,15} Although these instruments are not diag-
nostic in and of themselves, they do enable the clini-
cian to identify patients for more in-depth evaluation
as well as to monitor the progress of treatment.

**DIFFERENTIAL DIAGNOSIS**

The differential diagnosis of depression requires
consideration of a variety of other conditions, both psy-
chiatric and medical. Table 3 is a list of commonly en-
countered conditions often mistaken for major de-
pression.

**Psychiatric Conditions**

Anxiety disorders share many symptoms with major
depression. These include nervousness, poor concen-
tration, and poor sleep. However, anxiety disorders usu-
ally lack symptoms of a severely depressed mood and
feelings of helplessness, hopelessness, and worthless-
ness.\textsuperscript{16}

Attention-deficit/hyperactivity disorder can present
with poor concentration and restlessness. However, a
careful school history, as well as a screening for other
symptoms, is usually helpful in clarifying the diagnosis.

A number of other disorders, such as adjustment dis-
order with depressed mood and bereavement, can be
confused with major depression. However, despite the
intensity of symptoms, patients usually recover sponta-
neously within an expected period of time without spe-
cific treatment. A failure to improve or the progression
of symptoms, especially the development of suicidal
ideation or psychosis, warrants a consideration of major
depression.

Patients with schizophrenia or dementing disorders
such as Alzheimer's disease frequently present with
symptoms of depression. These patients are aware on
some level of their loss of function and articulate this in
terms of feeling depressed.

It is imperative to question patients with major de-
pression about previous manic or hypomanic episodes.
Patients with bipolar disorder are at risk for shifting
into a manic state when treated with an antidepressant
alone and require the addition of a mood-stabilizing
agent such as lithium, valproic acid, carbamazepine, or
gabapentin.\textsuperscript{17}

Women with premenstrual dysphoric disorder may
have symptoms that mimic major depression. However,
a careful history of the fluctuating nature of these symp-
toms can usually help clarify the diagnosis.

Patients with substance use disorders present a diag-
nostic challenge for many reasons. In many cases, pa-
tients begin using drugs as a means of self-medication
for their depressive symptoms. On the other hand, alco-
hol and various other drugs can cause a substance-
induced mood disorder with symptoms that mimic
those seen in major depression. A careful longitudinal
history as well as an assessment of the patient off alco-
hol and all drugs for at least 1 month is necessary to
help clarify the diagnosis.

**Medical and Neurologic Causes**

Depressive symptoms can be caused by a wide range
of medical and neurologic conditions. Common medi-
cal conditions with depressive manifestations include
thyroid and adrenal abnormalities, infectious diseases
such as mononucleosis and AIDS, inflammatory disor-
ders, vitamin deficiencies, cardiopulmonary disease,
renal disease, and systemic neoplasms. Neurologic con-
ditions that commonly include depressive manifesta-
tions include Parkinson's disease, Alzheimer's disease,
stroke, tumors, and seizure disorders. It is vital to screen all patients with depressive symptoms by doing a thorough medical and neurologic evaluation, including routine blood and urine tests.

**Pharmacologic Causes**

Pharmacologic agents often cause depressive symptoms as a side effect. Common offenders include antihypertensive agents, steroids, sedatives, hypnotics, antibiotics, analgesics, and antineoplastic agents.

**DIAGNOSIS OF CASE PATIENT**

The patient described in the case presentation meets the full diagnostic criteria for major depression. Diagnosis is based on this patient's significantly depressed mood and loss of interest in pleasurable activities for approximately 3 years. Associated symptoms include weight loss, poor sleep, low energy, feelings of worthlessness, and recurrent thoughts of death. His symptoms cause him impairment in his social functioning, as evidenced by his isolation from family and friends.

Because the patient has been totally clean from drugs for more than 6 years, his symptoms appear to be unrelated to the effects of any substance use. Although medical conditions such as being HIV positive can physiologically influence mood, his disease is reported to have been remarkably stable for some time and is thus unlikely to be a contributing factor.

When first diagnosed with HIV 12 years earlier, this patient likely met criteria for an adjustment disorder with depressed mood. Despite his feeling desperate and suicidal at the time, his symptoms quickly subsided without treatment as he began to accept his diagnosis and get on with his life.

**IV. PATHOPHYSIOLOGY OF DEPRESSION AND ANXIETY**

- Which neurotransmitter systems have been implicated in the pathophysiology of depression and anxiety?
- How does the neurobiology of depression and anxiety affect their treatment?

**NEUROBIOLOGY**

Many studies have demonstrated that dysregulation of biogenic amines plays a central role in the pathophysiology of depression. Furthermore, abnormalities of the neuroendocrine and neuroimmunologic systems point to a far-reaching and dynamic interrelationship between these systems.

**Regulation of Biogenic Amines**

Although the neurotransmitters norepinephrine and serotonin have been the most widely studied in depression, increasing evidence also points to significant roles for dopamine and acetylcholine in mood disorders.

Basic scientific studies have demonstrated an association between antidepressant response and the down-regulation of adrenergic receptors. Presynaptic β2-adrenergic receptors show a decrease in the amount of norepinephrine released when stimulated. Some tricyclic antidepressants, for example, are almost purely noradrenergic in their mechanism of action.

The depletion of serotonin is a common finding in depressed patients. The central role of serotonin in depression is illustrated by the usefulness of serotonergic medications in the treatment of depression. These agents act primarily through the blockade of serotonin reuptake to increase serotonin pools. As more subtypes of the serotonin receptor are discovered, more specific agents can be developed.

Current data suggest that dopaminergic activity might be reduced in depression. This is supported by the fact that drugs such as reserpine that reduce dopaminergic activity result in depressive symptoms, whereas bupropion and other drugs that increase dopamine activity are effective in reducing these symptoms.

Anxiety, on the other hand, appears to be mediated through the norepinephrine, serotonin, and γ-aminobutyric acid (GABA) neurotransmitter systems. This overlap accounts for the effectiveness of some antidepressants in treating both depression and anxiety.

**Table 4** provides a brief overview of some antidepressant medications and their neurotransmitter systems and neuroreceptors involved in their mechanism of action.

**Neuroendocrine Regulation**

The neuroendocrine system receives many neuronal inputs via biogenic amine neurotransmitters. While adrenal, thyroid, and growth hormone abnormalities are those most closely linked with mood disorders, melatonin, prolactin, follicle-stimulating hormone, luteinizing hormone, and testosterone abnormalities have been implicated as well.

**Neuroimmunologic Regulation**

Immunologic abnormalities have been reported in depressed and grieving patients. These abnormalities
are frequently secondary to dysregulation within the neuroendocrine system.

V. COMORBID DISORDERS

- What comorbid disorders should the clinician be aware of when evaluating depression?

ANXIETY DISORDERS

Given the tremendous overlap between depressive and anxiety disorders, it is often helpful to establish a longitudinal time course to determine which, if any, disorder is primary. Approximately 30% of patients with major depression meet the criteria for generalized anxiety disorder (Table 5), with the anxiety symptoms preceding the depressive symptoms in approximately half the cases. The risk for a major depressive episode increases in patients with a preexisting anxiety disorder.

Approximately 10% to 20% of patients with major depression have concurrent panic disorder. The combination of these two disorders usually results in greater impairment than either disorder alone.

Up to one third of patients with obsessive-compulsive disorder (OCD) meet the criteria for major depression, and another third experience depressive symptoms without meeting the full criteria. Obsessive-compulsive patients are likely to have a family history of depression. Frequently, it is the presence of OCD symptoms that brings a depressed patient in for treatment.

SUBSTANCE USE DISORDERS

The relationship between substance use disorders and depression is a difficult and complex one. On one hand, one third to one half of opioid users and 40% of patients with alcohol use disorders meet criteria for major depression at some point during their lives. On the other hand, the question of which disorder preceded the other raises many diagnostic and treatment dilemmas. Given the possibility that the mood symptoms reflect the toxic effects of the substance being used, the general rule of thumb is that when in doubt, it is prudent to wait until the individual is totally clean or sober for 1 or 2 months before diagnosing major depression.

EATING DISORDERS

One third to one half of patients with anorexia nervosa or bulimia nervosa suffer from comorbid depression. When both are present, the eating disorder is usually the principle target of treatment.

VI. TREATMENT

- What is the optimal approach to the treatment of major depression?
- What are the advantages and disadvantages of the various classes of antidepressant medications?
- What factors contribute to a less than optimal response to treatment?

APPROACH TO TREATMENT

Successful treatment does not begin with the taking of the first pill or even with a referral for psychotherapy or electroconvulsive therapy. Rather, it begins with a sense of hope and optimism conveyed by the clinician at the time of assessment. Eighty percent to 90%

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Table 4. Neurotransmitter Reuptake and Neuroreceptors Involved in the Actions of Antidepressants

<table>
<thead>
<tr>
<th>Drug</th>
<th>5-HT Reuptake</th>
<th>NE Reuptake</th>
<th>DA Reuptake</th>
<th>5-HT_{2A}</th>
<th>5-HT_{2C}</th>
<th>5-HT_{3}</th>
<th>α_{1}</th>
<th>α_{2}</th>
<th>Histamine_{1}</th>
</tr>
</thead>
<tbody>
<tr>
<td>SSRI*</td>
<td>✓</td>
<td></td>
<td></td>
<td></td>
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<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Bupropion</td>
<td>✓</td>
<td></td>
<td></td>
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<tr>
<td>Venlafaxine</td>
<td>✓</td>
<td>✓</td>
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<tr>
<td>Nefazodone</td>
<td>✓</td>
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<td></td>
<td>✓</td>
<td></td>
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<tr>
<td>Mirtazapine</td>
<td>✓</td>
<td>✓</td>
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</tr>
<tr>
<td>Reboxetine</td>
<td>✓</td>
<td></td>
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</tr>
</tbody>
</table>

DA = dopamine; 5-HT = serotonin; NE = norepinephrine; SSRI = selective serotonin reuptake inhibitor.

*SSRI comprises fluoxetine, sertraline, paroxetine, fluvoxamine, and citalopram.

of patients with major depression have a successful outcome given an adequate course of treatment.

Beyond any specific treatment, the patient's physician or psychiatrist plays a unique role in establishing a framework for treatment. This process is called psychoeducation. Patients must be taught that their condition is a medical illness that requires medical treatment and is not something under their willful control. Patients need help in alleviating the guilt and self-blame that frequently accompany depression. Patients also need to have their questions answered and doubts and fears addressed: “What can I expect?” “How long will treatment last?” “What are the side effects?” “When can I expect to feel better?” “Is the medication addictive?” Even if a patient does not articulate these questions, he or she nevertheless deserves to have them answered and will be comforted by the answers.

Patients recover from an episode of major depression in stages, usually over the course of 4 to 6 weeks. Poor sleep and appetite loss are the first symptoms to improve. Next, patients typically experience an improvement in their energy levels. A subjective feeling of improved mood is usually the last symptom to be resolved. This sequence should be explained to patients at the start of treatment.

Patients with suicidal ideation are at particular risk during the initial stages of treatment, as they may now have the energy to carry out any plans before they experience a true improvement in their mood.

Although medication and psychotherapy individually have been shown to be efficacious, repeated studies have demonstrated the added benefit of a combined approach to treatment, addressing the biologic aspects of the disease as well as environmental and psychodynamic factors.

**ELECTROCONVULSIVE THERAPY**

Electroconvulsive therapy (ECT) is probably one of the most effective yet misunderstood treatments in the field of medicine. It involves the application of either a unilateral or bilateral electrical stimulus to the head for the purpose of inducing a controlled seizure. The exact mechanism of action is unknown. Nevertheless, ECT is an extremely safe and often life-saving procedure because of its rapid effectiveness and few side effects. The only absolute contraindication to ECT is the presence of increased intracranial pressure.18

**PSYCHOTHERAPY**

Several specific types of psychotherapy have been found to be effective in treating depression. These include behavioral therapy, which addresses maladaptive behaviors; cognitive therapy, which focuses on correcting cognitive distortions; and interpersonal therapy, which looks in depth at problematic interpersonal relationships.19,20 These therapies generally involve an active therapeutic approach and specific goals for treatment.

**Table 5. DSM-IV Diagnostic Criteria for Generalized Anxiety Disorder**

| A. | Excessive anxiety and worry (apprehensive expectation), occurring more days than not for at least 6 months, about a number of events or activities (such as work or school performance). |
| B. | The person finds it difficult to control the worry. |
| C. | The anxiety and worry are associated with 3 or more of the following 6 symptoms (with at least some symptoms present for more days than not for the past 6 months). Note: only 1 item is required in children. |
| (1) | Restlessness or feeling keyed up or on edge |
| (2) | Being easily fatigued |
| (3) | Difficulty concentrating or mind going blank |
| (4) | Irritability |
| (5) | Muscle tension |
| (6) | Sleep disturbance (difficulty falling or staying asleep, or restless unsatisfying sleep) |
| D. | The focus of the anxiety and worry is not confined to features of an Axis I disorder (eg, the anxiety or worry is not about having a panic attack [as in panic disorder], being embarrassed in public [as in social phobia], being contaminated [as in obsessive-compulsive disorder], being away from home or close relatives [as in separation anxiety disorder], gaining weight [as in anorexia nervosa], having multiple physical complaints [as in somatization disorder], or having a serious illness [as in hypochondriasis]), and the anxiety and worry do not occur exclusively during posttraumatic stress disorder. |
| E. | The anxiety, worry, or physical symptoms cause clinically significant distress or impairment in social, occupational, or other important areas of functioning. |
| F. | The disturbance is not due to the direct physiological effects of a substance (eg, a drug of abuse, a medication) or a general medical condition (eg, hyperthyroidism) and does not occur exclusively during a mood disorder, a psychotic disorder, or a pervasive developmental disorder. |

Selective Serotonin Reuptake Inhibitors

Selective serotonin reuptake inhibitors (SSRIs) have largely replaced tricyclic antidepressants (TCAs) as the drugs of first choice by virtue of their ease of use, safety in overdose, and their overall better side-effect profile. SSRIs lack the anticholinergic, antihistaminic, and anti-α-adrenergic effects associated with TCAs. Common side effects of SSRIs include nausea, dizziness, headache, loose stools, insomnia, decreased appetite, and sexual dysfunction.

In addition to treating depression, the SSRIs are useful in a variety of other conditions including panic disorder, OCD, social phobia, and bulimia nervosa. Fluoxetine (Prozac), sertraline (Zoloft), paroxetine (Paxil), fluvoxamine (Luvox), and citalopram (Celexa) are the SSRIs currently available in the United States.

Tricyclic Antidepressants

The TCAs are another group of effective antidepressants. However, in contrast to the SSRIs, the TCAs must be started at a relatively low dose and gradually titrated up to a therapeutic level. Anticholinergic side effects include dry mouth, blurred vision, constipation, tachycardia, and urinary retention. Blockade of histamine1 receptors can cause sedation and weight gain. α-Adrenergic receptor blockade can cause orthostatic hypotension and dizziness. Quinidine-like cardiac effects can cause conduction abnormalities; for this reason, patients receiving TCAs should undergo an electrocardiogram before the start of treatment and periodically after treatment has begun. It should be noted that the TCAs can be lethal in overdose.

Monoamine Oxidase Inhibitors

Monoamine oxidase inhibitors (MAOIs) are used largely in treatment-resistant patients or in those with psychotic depressions. They require a tyramine-free diet as well as careful monitoring of drug interactions. The major risk factor associated with MAOIs is the development of a potentially lethal hypertensive crisis.

Novel Antidepressants

Over the past several years, a number of novel antidepressants that do not fit neatly into any one category have been developed. These include venlafaxine (Effexor), nefazodone (Serzone), mirtazapine (Remeron) and bupropion. The concept behind these drugs is an attempt to increase the quantity of deficient neurotransmitters, often in different systems simultaneously, while minimizing distressing side effects.

Phototherapy

Artificial bright light or phototherapy has been demonstrated to be an effective means of treatment for patients suffering from seasonal affective disorder. It involves exposure to a high-intensity light for 2 to 3 hours daily during the fall and winter months. One theory is that the light therapy causes a phase advance of the delayed circadian rhythms that occur in this form of depression.

Hospitalization

Hospitalization is indicated for patients who present a risk to themselves by virtue of being actively suicidal, or who are unable to properly care for themselves in their home environment. Areas to be assessed in deciding on hospitalization include the patient's support network, ability to meet basic needs, ability to make rational decisions, and the presence of psychotic features. Severely depressed patients with pressing medical needs should be considered candidates for admission.

Treatment of Case Patient

The treatment of the patient described in the case presentation follows a 2-pronged approach. Given the duration and severity of his symptoms, a trial of an antidepressant medication is certainly indicated. This patient would also benefit from a psychotherapeutic approach that would include psychoeducation and supportive therapy administered by the treating physician. If more involved dynamic issues become apparent, the patient can be referred to a trained therapist for further assessment and treatment.

Although all currently available antidepressant medications are thought to be equally effective, the SSRIs have become the drugs of first choice in treating depression. However, many other considerations must be taken into account when choosing an agent. These include the side-effect profile of the medication, the need to choose an activating or sedating agent, the safety of the medication in overdose, metabolism of the medication (ie, liver versus kidney), the likelihood of drug interactions, and the need for dose titration. The dose schedule is another very important factor. Compliance is improved in patients taking medication once a day as opposed to multiple times daily.

Given the stigma attached to this patient's medical illness and recognizing his further social withdrawal resulting from his depression, every effort must be made by the clinician to bolster this patient's support network. This may be accomplished by various means, ranging from direct family involvement in the patient's care to referral to an outside support group.
VII. SUICIDE

Approximately two thirds of depressed patients harbor suicidal thoughts. Up to 15% of severely depressed patients will eventually succeed in killing themselves. Risk factors for suicide include alcohol and drug use, intense states of anxiety, the presence of psychotic features (particularly command auditory hallucinations), concurrent medical illness, recent personal loss, poor social supports, unemployment, a history of suicide in close relatives, and previous suicide attempts. Women attempt suicide 4 times more often than men; however, men are 3 times more likely than women to succeed in their attempt. Demographically, older white men are at particularly high risk.

Contrary to popular belief, patients typically experience a sense of relief when asked about their suicidal thoughts, especially when these feelings are validated and given room for expression. There is no evidence to suggest that asking about suicidal ideation increases the risk of suicide.

BOARD REVIEW QUESTIONS

Choose the single best answer to each of the following questions.

Questions 1 and 2 refer to the following case study.

A 21-year-old woman is referred to you by her family for evaluation. She broke up with her fiancé last week and has since quit her job and started giving away some of her possessions.

1. Regarding the possibility of suicide, you should:
   A) Avoid bringing up the subject on the first visit because it may get in the way of establishing a therapeutic relationship with her
   B) Initiate treatment with a selective serotonin reuptake inhibitor (SSRI) immediately, realizing that it is safe in case of overdose
   C) Not worry about suicide because demographically the patient is at low risk
   D) Ask the patient about any suicidal ideas or plans in a concerned but direct manner on the initial visit
   E) Ask her in an oblique manner why she quit her job and gave away her possessions, but avoid asking her directly about suicide

2. Which of the following items would factor into a decision to hospitalize this patient at this time?
   A) A history of previous suicide attempts
   B) Poor relationships with her family
   C) A history of alcohol abuse
   D) The presence of command auditory hallucinations
   E) All of the above

3. The typical sequence of improvement in a patient recovering from an episode of major depression is:
   A) Mood, energy level, and vegetative symptoms (eg, sleep, appetite) improve simultaneously 2 to 4 weeks after treatment has started
   B) Mood improves first, followed by energy level, followed by sleep and appetite
   C) Sleep and appetite improve first, followed by mood, followed by energy level
   D) Energy level improves first, followed by sleep and appetite, followed by mood
   E) Sleep and appetite improve first, followed by energy level, followed by mood

4. Common side effects of SSRIs include:
   A) Nausea, headache, and insomnia
   B) Blurred vision, dry mouth, and constipation
   C) Hypertensive crisis
   D) Quinidine-like conduction abnormalities
   E) Sedation and weight gain

5. All of the following neurotransmitters are involved in the neurobiology of depression EXCEPT:
   A) Norepinephrine
   B) Dopamine
   C) Serotonin
   D) γ-aminobutyric acid

   For question 6, more than one answer may be correct.

6. A 45-year-old woman is under your care for an initial episode of major depression. You start her on extended-release venlafaxine 37.5 mg once a day. After 3 months, she reports only minimal improvement. Your best course of action at this time includes which of the following?
   A) Immediately switch her to an SSRI
   B) Stop her medication while you reconsider her diagnosis
   C) Increase her dose of medication up to 75 mg/day and continue to observe
   D) Add a low dose of a tricyclic antidepressant to her regimen
   E) Assess for poor compliance due to side effects or lack of understanding regarding how she is to take the medication


