

The Evaluation and Treatment of Depression in Primary Care

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The evaluation and treatment of depressive disorders are vital functions for practicing primary care physicians. Depression is a prevalent, recurrent, highly treatable disorder that is debilitating and leads to significant psychosocial impairment. In view of the broadly available armamentarium of safe, newer medications, primary care physicians should be proficient in the treatment of these disorders. The following review will provide a synopsis of the current state of diagnosis, evaluation, and treatment of depression in the primary care setting. Appropriate treatment of depression can result in improvement in emotional, cognitive, and behavioral symptoms of depression and reduce psychosocial impairment, disability, and associated medical morbidity.

DEPRESSION IN PRIMARY CARE

Depressive disorders are highly prevalent illnesses that cause significant disability, psychosocial impairment, increased health care utilization, morbidity, and mortality. According to the National Comorbidity Survey, the lifetime prevalence of major depression in the general US population is 17.1%; in women, this figure rises to 21.3% (1). The disability caused by depression is comparable with the degree of disability related to other chronic medical conditions such as hypertension, diabetes, and arthritis. Depressive disorders are frequently associated with significant and pervasive impairments in social functioning, causing enormous personal, social, and economic burden (2). Furthermore, depression is associated with morbidity and mortality related to other medical condi-

tions, as demonstrated by recent evidence that depression is a major risk factor for both the development of cardiovascular disease and death after an index myocardial infarction (3).

Major depression is almost twice as likely to occur in women and has a peak age of onset between 20 and 40 years. Nonetheless, depression is widespread among the elderly as well. Depression in late life is a serious public health concern, and comorbidity of depression with other illnesses is particularly problematic in older persons (4). Depression is most often a recurrent disorder (5).

Due to advances in psychopharmacologic treatment, depression is a highly treatable illness. Unfortunately, there exists overwhelming evidence that individuals with depression are being seriously

undertreated (6), causing substantial costs to individuals and society. The alleviation of suffering and impairment associated with depression can be quite gratifying to the primary care physician who is astute and proficient in the evaluation and treatment of highly prevalent and debilitating psychiatric disorders.

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In the busy office practices of primary care providers, diagnosing depression can sometimes be complicated because of the multitude of signs and symptoms with which the depressed patient can present. For example, the initial presentation of a patient with clinically significant depression can include a broad range of symptoms, from somatic complaints (fatigue, insomnia, anorexia, or various nonspecific somatic symptoms) to emotional concerns (sadness, anxiety, or feelings of guilt) and other problems (difficulty at work, marital problems, irritability, or memory impairment). Although many patients are treated for depression in the primary care setting, the clinician should also be able to determine when psychiatric referral is indicated.

ESTABLISHING THE DIAGNOSIS

Major depression is a syndrome consisting of a group of signs and symptoms. Currently, psychiatric diagnosis is accomplished following the criteria listed in the *Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition, Text Revision* (7). According to this standardized descriptive approach to diagnosis, a major depressive episode is defined as a 2-week period during which 5 of 9 symptoms are present, representing a change from previous functioning (**Table I**). Symptoms of a

major depressive episode include depressed mood/sadness/tearfulness, diminished interest or pleasure (anhedonia), change in weight or appetite, insomnia or hypersomnia, psychomotor agitation or retardation, fatigue or loss of energy, feelings of worthlessness or inappropriate guilt, diminished ability to concentrate or indecisiveness, and suicidal ideation. The diagnosis of major depressive disorder refers to the presence of a major depressive episode, whereas dysthymic disorder indicates a syndrome of milder symptoms and protracted duration (at least 2 years). In the clinical setting, having patients complete a brief self-administered screening tool may facilitate the diagnosis of depression (8). Such scales include the Beck Depression Inventory (21 multiple-choice items) (9), and the 20-item Zung Self-Rating Depression Scale (10).

EVALUATION AND DIFFERENTIAL DIAGNOSIS

Before making a diagnosis of major depressive disorder or dysthymic disorder, a search for medical causes of the depressive disorder should be conducted. Medical conditions that are known to be physiologically related to the symptoms of depression include endocrinopathies (eg, hypo-

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thyroidism), neurologic disorders (eg, stroke, neurosyphilis), and many others (**Table II**). Additionally, a variety of substances of abuse can be causally implicated in the presentation of depression. These include alcohol, sedatives, and cocaine. Iatrogenic causes of depression include antihypertensives that alter central biogenic amine pathways (β -blockers, reserpine, methyl dopa, guanethidine, clonidine), corticosteroids, antineo-

TABLE I.

SUMMARY OF DSM-IV-R CRITERIA FOR MAJOR DEPRESSIVE EPISODE (7)

- 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.
- (1) Depressed mood most of the day, nearly every day, as indicated by either subjective report or observation made by others
 - (2) Markedly diminished interest or pleasure in all, or almost all, activities most of the day, nearly every day
 - (3) Significant weight loss when not dieting or weight gain, or decrease or increase in appetite nearly every day
 - (4) Insomnia or hypersomnia nearly every day
 - (5) Psychomotor agitation or retardation nearly every day
 - (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
 - (8) Diminished ability to think or concentrate, or indecisiveness, nearly every day
 - (9) Recurrent thoughts of death (not just fear of dying), recurrent suicidal ideation without a specific plan, or a suicide attempt or 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 physiologic effects of a substance or general medical condition.
- E. The symptoms are not better accounted for by bereavement, ie, 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.

DSM-IV-R = Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition, Text Revision.
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plastics, interferon- α , and, possibly, isotretinoin. Whether the depression is substance induced or caused by a general medical condition, the underlying cause should be treated, but if improvement in depressive symptoms fails to occur after approximately 4 to 6 weeks, the depression should be independently diagnosed and treated (8).

After the exclusion of the aforementioned causes of depression, the clinician can consider primary psychiatric conditions associated with depressive symptoms. The distinction between unipolar depression (a major depressive episode in a patient with no history of hypomania or mania) and bipolar depression (a major depressive episode in a patient with a history of hypomania or mania) is of vital importance and significantly affects decisions involved in treatment planning. (Symptoms of hypomania and mania include elevated/expansive/

irritable mood, inflated self-esteem or grandiosity, decreased need for sleep, flight of ideas or racing thoughts, distractibility, increase in goal-directed activity, pressured speech, and excessive involvement in pleasurable activities.) Patients with bipolar depression are more likely to experience a switch to hypomania or mania or an acceleration in cycling during treatment with an antidepressant in the absence of concomitant treatment with a mood stabilizer. Family history of unipolar and bipolar disorders should also be reviewed. Women have an increased incidence of depression during times of hormonal change, including pregnancy and the postpartum period. Primary anxiety disorders should also be considered in the differential diagnosis of depression. In older adults, depression with cognitive impairment that is reversed by antidepressant treatment may be a predictor of the

TABLE II.

MEDICAL CONDITIONS PHYSIOLOGICALLY ASSOCIATED WITH DEPRESSION

Endocrine Disorders

- Hypothyroidism
- Hyperthyroidism
- Parathyroid disorders
- Cushing's syndrome

Neurologic Disorders

- Cerebrovascular accidents
- Central nervous system (CNS) lesions
- Neurosyphilis
- Multiple sclerosis
- Neurosarcoidosis
- CNS vasculitis
- HIV-associated CNS pathology

Other Disorders

- Vitamin deficiencies (eg, folate and vitamin B₁₂)
- Anemia
- Hypoxia
- End-stage renal disease
- Systemic lupus erythematosus and other connective tissue diseases
- Occult malignancy (eg, pancreatic cancer)

development of an irreversible dementia (4), although the “pseudodementia” of depression should not be mistaken for a primary dementia. “Double depression” can occur in an individual with a major depressive disorder superimposed on a chronic dysthymic disorder. Many patients with personality disorders can present with symptoms of depression, and an assessment of the longitudinal history of the symptoms is vital in establishing the correct diagnosis.

During any evaluation of depressive symptoms, the clinician should fully evaluate the history of symptoms; the duration, number, and severity of current symptoms; and the presence of associated syndromes, including anxiety, psychosis, substance abuse, and suicidality. A thorough evaluation of past and current suicidal thoughts, plans, intent, and actions should be assessed. Additionally, the clinician should keep in mind potential risk factors for suicide (**Table III**) when assessing and documenting suicide risk. The incidence of suicidality during depression is likely increased by the presence

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of anxiety, psychosis, and substance abuse. Of patients with untreated recurrent major depression, 15% will die by suicide.

Accurate diagnosis can only be accomplished by obtaining a medical and psychiatric history, performing a physical examination and mental status examination (**Table IV**), and ordering laboratory tests to rule out other medical conditions that can cause depression. A standard laboratory evalu-

TABLE III.

POTENTIAL RISK FACTORS FOR SUICIDE IN MAJOR DEPRESSION

Demographic Factors

- Male gender
- White race
- Aged 24 to 35 or >50 years

Factors Associated with the Depressive Episode

- Suicidal thoughts or acts
- Lack of treatment or inadequate treatment of depressive episode
- Presence of hopelessness
- Low self-esteem, feelings of failure
- More severe depressive symptoms (diminished concentration, insomnia, anhedonia, but not diminished energy level)
- Recent bereavement
- Presence of psychosis
- Concomitant anxiety or panic attacks
- Being in the first 3 months after the onset of the depressive episode

Factors Related to Personality Characteristics

- Personality variables including aggression, hostility, or impulsiveness

Comorbidity

- Comorbid substance use disorders
- Comorbid borderline personality traits or disorder
- Comorbid conduct disorder or antisocial personality traits or disorder
- Comorbid general medical conditions
- Bipolar disorder or mood cycling
- Acute substance intoxication

Factors Revealed by History

- History of suicide attempt
- History of taking precautions against being discovered after an attempt
- Presence of a family history of suicide
- Early onset of depression, being younger at first hospitalization, more previous hospitalizations
- Parental loss through death before the age of 11
- Childhood history of physical or sexual abuse
- Corporal punishment in adolescence

Psychosocial Factors

- Being recently widowed/separated/divorced
- Chronic physical illness
- Social, financial, or family crisis or loss (negative life events)
- Unemployment or financial problems
- Lack of religious or moral constraints against suicide
- Not living with a child younger than 18
- Social isolation

Miscellaneous

- Access to means with greater lethality
- Contagion or recent exposure to suicide

KEY POINT

Accurate diagnosis can be accomplished only by obtaining a medical and psychiatric history, performing a physical examination and mental status examination, and ordering laboratory tests to rule out other medical conditions that can cause depression.

ation includes complete blood counts, basic chemistries, hepatic and renal function tests, thyroid function tests, folate and vitamin B₁₂ levels, urinalysis, urine drug screen, syphilis serology, and HIV testing. These tests are the same laboratory studies used to work up dementia.

GOALS OF TREATMENT

Unfortunately, many cases of depression are undiagnosed or inadequately treated. The primary goal of treatment should be full remission of all depressive symptoms. Partial remission is not an acceptable outcome. The continuation and maintenance phases are important aspects of treatment (11), due to the risk of relapse and recurrence (Table V).

The rate of recurrence following a single episode of major depression is approximately 50%. This percentage increases with each subsequent episode of depression and in patients with a family history of affective disorders. In patients with a history of >3 episodes, indefinite therapy with an antidepressant should be seriously considered because of the very high risk of recurrence (5). Compliance should be encouraged and monitored. Factors that may affect a patient's adherence to the medication regimen include the complexity and side-effect burden of the antidepressant regimen; substance abuse; and poor or incomplete understanding of symptoms, illness, and treatment.

When initiating treatment with an antidepressant, the patient should be provided with details of the risks, benefits, and alternatives of treatment. Efficacy of antidepressants should be presented, and side effects should be reviewed. Informing patients in advance about side effects that may

occur and offering reassurance are important therapeutic tasks to be done at the beginning of every treatment so that patients will not be frightened and will be more tolerant of side effects (12). The patient should be advised that recovery will be a gradual process and that antidepressants typically take several weeks before a therapeutic effect is evident. Treatment is recommended to last 4 to 6 weeks before a decision regarding efficacy can be made. Improvement may be variable, with some symptoms improving before others, and the patient may experience occasional days of increased symptoms during the course of recovery. Improvement of the illness should not be interpreted by patients or physicians as an indicator that antidepressants are no longer necessary. The continuation phase of treatment consists of 16 to 20 weeks of continued treatment (with the antidepressant used in the acute phase) following remission, with the goal of preventing relapse. Maintenance phase treatment should be considered to prevent recurrence, based on the patient's longitudinal history and severity of illness. Maintaining antidepressant medication at the dosage used to treat the acute episode is an effective means of preventing recurrence (13).

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PHARMACOTHERAPY

Blockade of monoamine (serotonin and norepinephrine) transport is the primary cellular action associated with many antidepressant medications, and chronic administration of all antidepressants increases the efficiency of serotonergic transmission in the synapse, albeit by different mechanisms (14). The pharmacotherapy of depression was initiated in the 1950s with the advent of the

TABLE IV.

FINDINGS ON THE MENTAL STATUS EXAMINATION SUGGESTIVE OF DEPRESSION

- **Appearance:** diminished self-care and grooming, quiet and withdrawn stance
- **Attitude:** irritability, restlessness, sadness
- **Behavior:** diminished eye contact, stooped posture, hand-wringing, psychomotor slowing or agitation
- **Speech:** increased response latency, decreased rate and rhythm of speech
- **Mood:** down, depressed, sad, unhappy, empty, helpless, hopeless
- **Affect:** sad, emotionally blunted, tearful, anxious
- **Thought processes:** slow thoughts, fewer expressed thoughts
- **Thought content:** excessive and inappropriate guilt; thoughts of worthlessness, hopelessness, or helplessness; mood-congruent psychotic features (hallucinations or delusions); suicidal thoughts, intent, plans, or acts
- **Insight/judgment:** impaired to good
- **Cognition:** impairment in memory, attention, and concentration

monoamine oxidase inhibitors (MAOIs). Shortly thereafter, the tricyclic antidepressants (TCAs) were discovered to be efficacious in the treatment of depression.

Currently, MAOIs (phenelzine, isocarboxazid, and tranylcypromine) are rarely used. Their use is complicated by side effects (including hypotension), lethality in overdose, and lack of simplicity in dosing. Patients treated with MAOIs must follow a specific tyramine-free diet because of the potential for a pharmacodynamic interaction with tyramine that can cause a hypertensive crisis. Nonetheless, these medications may be particularly useful in the treatment of so-called atypical depression (hypersomnia, hyperphagia), although their use is best handled by psychiatrists who have experience prescribing them.

The agents in the TCA class of antidepressants can be subdivided into the tertiary amines (amitriptyline, imipramine, clomipramine*) and the secondary amines (desipramine, nortriptyline). The use of TCAs is limited by their relatively unfavorable side-effect profile (largely due to anticholinergic, antiadrenergic, and antihistaminic properties), narrow therapeutic index, and lethality in overdose (due to inhibition of sodium channels that causes slowing of cardiac conduction and potentially fatal arrhythmias), as well as the need to titrate the dose.

*Not FDA-approved for the treatment of depression.

Although these medications are still occasionally used in refractory cases, their use should be limited to practitioners with experience using them while monitoring electrocardiographic changes and performing therapeutic blood monitoring. Secondary

KEY POINT

The vast majority of cases of depression can be treated with SSRIs and other newer antidepressant medications.

amine TCAs are more selective at norepinephrine reuptake inhibition and cause fewer side effects, rendering them more widely used than the tertiary amines; they do, however, exhibit the same properties of toxicity.

The vast majority of cases of depression can be treated with selective serotonin reuptake inhibitors (SSRIs) and other newer antidepressant medications. Information about the patient's medical history and personal or family history of response provides predictive data about future response and side effects (8). The SSRIs (fluoxetine, paroxetine, sertraline, fluvoxamine*, and citalopram) are efficacious in treating depression and many primary anxiety disorders (obsessive-compulsive disorder, panic disorder, posttraumatic

TABLE V.

DEFINITIONS OF TERMS RELATED TO THE COURSE OF DEPRESSION (21)

- **Episode:** A period lasting longer than 2 weeks (as defined by the *DSM-IV-R*) during which the patient is consistently within the fully symptomatic range of a sufficient number of symptoms to meet syndromal criteria for the disorder. For the clinician, this typically triggers a decision to treat.
- **Partial remission:** A period during which an improvement of sufficient magnitude is observed that the individual is no longer fully symptomatic (ie, no longer meets syndromal criteria for the disorder but continues to evidence more than minimal symptoms). If a partial remission fails to become a full remission after a reasonable period, the clinician will typically alter treatment (by increasing the intensity of the current treatment or by augmentation).
- **Response:** The point at which a partial remission begins. A response, unlike a partial remission, does require treatment and thus implies that the cause of the change in the patient's condition is known, which may not be a valid assumption.
- **Full remission:** A relatively brief period during which an improvement of sufficient magnitude is observed that the individual is asymptomatic (ie, no longer meets syndromal criteria for the disorder and has no more than minimal symptoms). No increase in the intensity of the treatment regimen is required, although continuation treatment should be used to prevent relapse.
- **Recovery:** A remission that lasts for a specified period of time. The term is used to describe recovery from the episode, not the illness per se. In the clinical setting, a declaration of recovery raises the possibility that treatment can be discontinued or, if treatment is continued, the aim is prevention of a subsequent recurrence of an episode (maintenance treatment).
- **Relapse:** A return of symptoms satisfying the full syndrome criteria for an episode that occurs during the period of partial or full remission, but before recovery as defined above. A relapse signals a need for treatment intervention or modification of ongoing treatment.
- **Recurrence:** The appearance of a new episode of major depressive disorder occurring during a recovery. A recurrence implies the need for treatment and a revision in the history of the course of the illness. The latter may have prognostic and treatment implications. In studies of maintenance therapy, recurrence is typically the outcome of primary interest. The term relapse (*vidra supra*) represents the return of the symptoms of a still ongoing but symptomatically suppressed episode, whereas the term recurrence represents an entirely new episode.

DSM-IV-R = Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition, Text Revision.

Adapted with permission from Frank E, Prien RF, Jarrett RB, et al. Conceptualization and rationale for consensus definitions of terms in major depressive disorder. Remission, recovery, relapse, and recurrence. *Arch Gen Psychiatry.* 1991;48:851–855.

stress disorder, social phobia) and offer several important advantages. They require minimal dose titration, and the starting dose can sometimes be an effective dose (Table VI). Perhaps most importantly, these medications are safe in overdose. Because generic formulations of these medications are not yet available, they are more expensive than the older antidepressants, although this difference may not persist when other costs of using older antidepressants are considered. The SSRIs have a relatively mild side-effect burden. Sexual side effects of these medications (delayed ejaculation, anorgasmia, decreased libido) are being increasingly recognized and studied.

Clinicians using SSRIs and newer antidepressants should be familiar with their potential for pharmacokinetic drug-drug interactions resulting from the inhibition of various cytochrome P450 microsomal hepatic enzymes (15). Many of the newer anti-

depressants are associated with a risk for clinically significant drug interactions. Different SSRIs inhibit different isoenzymes of the hepatic cytochrome P450 system, leading to the potential for elevation in the blood level of the other medications.

Various symptoms have been associated with the abrupt discontinuation of SSRIs, including dizziness, paresthesia, asthenia, myalgias, nausea, loose stools, visual disturbances, irritability, insomnia, mood worsening, electric shock–like sensations in the upper extremities, and headache (16). Such discontinuation symptoms are more likely to occur with antidepressants with shorter half-lives as compared with fluoxetine, which has a long half-life. Tapering the antidepressant before discontinuation is recommended.

Other newer antidepressants include sustained-release bupropion, which may act on dopamine and norepinephrine systems; a serotonin

TABLE VI.

STARTING DOSAGES AND DOSAGE RANGES (DAILY) FOR FIRST-LINE ANTIDEPRESSANT AGENTS

<i>Generic Name (Trade Name)</i>	<i>Typical Daily Starting Dosage</i>	<i>Typical Daily Dosage Range</i>
Fluoxetine (Prozac®)	20 mg	20 mg–80 mg
Paroxetine (Paxil®)	20 mg	20 mg–50 mg
Sertraline (Zoloft®)	50 mg	50 mg–200 mg
Fluvoxamine (Luvox®)	50 mg	100 mg–300 mg
Citalopram (Celexa™)	20 mg	20 mg–60 mg
Venlafaxine (Effexor® XR)	37.5 mg	75 mg–375 mg
Bupropion (Wellbutrin SR®)	100 mg	100 mg–200 mg BID
Nefazodone (Serzone®)	100 mg	200 mg–600 mg
Mirtazapine (Remeron®)	15 mg	15 mg–45 mg

(5-HT)/norepinephrine reuptake inhibitor that is particularly effective in refractory and severe depression (extended-release venlafaxine); a 5-HT_{2A} receptor antagonist and 5-HT/norepinephrine reuptake inhibitor (nefazodone); and a 5-HT_{2A}, 5-HT_{2C}, and 5-HT₃ receptor antagonist, and an α₂-adrenergic receptor antagonist (mirtazapine) (Table VI). In addition to their FDA-approved indications for depression, sustained-release bupropion is also approved for smoking cessation and extended-release venlafaxine is approved for generalized anxiety disorder.

Patients presenting with a significant anxiety component to the depressive illness should be treated with the coadministration of an antidepressant and, at least initially, an anxiolytic such as clonazepam*, a long-acting benzodiazepine. Depression with associated psychotic features should be treated with an antidepressant and an antipsychotic medication—atypical antipsychotic agents such as risperidone, olanzapine, or quetiapine are currently the first-line choice—or with electroconvulsive therapy (ECT). Patients with bipolar disorder should be taking an optimal dose of a mood stabilizer medication (lithium, valproate, or carbamazepine†) before initiating therapy with an antidepressant (17).

In some cases, full remission will not be attained with the first trial of medication. If an ade-

quate trial of the initial antidepressant does not yield even a partial response after approximately 4 to 8 weeks, switching to an antidepressant from a different class should be tried (eg, switching from an SSRI to extended-release venlafaxine, sustained-release bupropion, nefazodone, or mirtazapine). However, true resistance to antidepressant therapy must be distinguished from inadequate dose, duration, or compliance with initial antidepressant therapy (18). When an initial partial response has been achieved, the dose of the antidepressant should be optimized. If full remission still does not ensue, an augmentation strategy can be tried. Reassessment of the diagnosis may reveal psychiatric comorbidity, the presence of depressive subtypes, or the possibility of a medical etiology. Augmentation agents include thyroid hormone (T₃)‡, lithium‡, psychostimulants (eg, methylphenidate‡, Dexedrine®‡, or modafinil‡), buspirone‡, and other antidepressants (18).

In older women, hormone replacement therapy‡ has been associated with improvements in mood and quality of life, but the data are still preliminary (4). Although many over-the-counter herbal preparations are being promoted for the treatment of depression (eg, St. John’s wort‡, or *Hypericum perforatum*), current data on the efficacy and safety of these agents are limited. In fact, some reports suggest potential drug-drug interactions when they are used in combination with pre-

*Not FDA-approved for the treatment of anxiety.

†Not FDA-approved for the treatment of bipolar disorder.

‡Not FDA-approved for the treatment of depression.

scribed medications. All patients should be questioned about the use of these medications while gathering history, due to the widespread use of herbal remedies and other modalities in complementary and alternative medicine.

KEY POINT

Careful attention should be given to the decision to treat on an outpatient basis versus psychiatric hospitalization (voluntarily or via civil commitment when necessary) in cases of severe or complicated depression.

OTHER TREATMENT METHODS

All treatment efforts should be supplemented with the establishment of a treatment alliance and comfortable rapport with the patient. Although motivation is often diminished, the patient should be encouraged to take an active role in the treatment planning. Psychoeducation should be provided relative to symptoms, the nature of the illness, the important role of medication (and that antidepressants are not addictive), potential side effects and adverse events, issues involved in compliance, and the course of the illness.

Psychotherapy is often useful as an adjunct to treatment of moderate to severe depression and may be useful as monotherapy in cases of mild depression. Several forms of psychotherapy have been demonstrated to be efficacious, including interpersonal therapy and cognitive-behavioral therapy. Combined treatment using both an antidepressant medication and psychotherapy has been shown to prevent or delay recurrence of major depressive episodes (19). Other forms of psychotherapy may be effective, including marital therapy, family therapy, and group therapy (11). Referral to an experienced psychotherapist should be considered by the physician managing the pharmacologic agents.

Hospitalization may be necessary for the treatment of some cases of severe depression. These circumstances include the presence of psychotic features, major comorbid medical condi-

tions, suicidality, or when functional impairment prevents the patient from adequately caring for basic needs. Careful attention should be given to the decision to treat on an outpatient basis versus psychiatric hospitalization (voluntarily or via civil commitment when necessary) in cases of severe or complicated depression.

ECT is likely the most efficacious treatment for severe depression and should be considered in patients with severe or refractory depression, depression during pregnancy, or with comorbid medical conditions precluding pharmacotherapy. In addition, ECT may also be helpful when serious suicidality, psychosis, or catatonia is present. ECT has been shown to be at least as effective as pharmacotherapy in short-term treatment for psychotic depression and should be considered as a potential strategy more frequently, especially in severe presentations and as a maintenance treatment (20).

KEY POINT

Referral to a psychiatrist is indicated for complex cases—those requiring combination therapy, augmentation strategies, hospitalization, or ECT—or in cases with complex medical, psychiatric, or substance use comorbidity.

Phototherapy and sleep deprivation are other somatic therapies that have been shown to be effective, although the use of these methods is limited by practical obstacles. Experimental treatments include rapid transcranial magnetic stimulation and vagus nerve stimulation.

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SUMMARY

Depression is a prevalent disorder that commonly presents masked by nonspecific physical concerns (eg, headaches, pain, gastrointestinal distress) or

problems other than a clearly expressed complaint of depressed mood. Because it is associated with significant impairment and disability in many domains, depression should be adequately diagnosed and fully treated. Evaluation of depressive symptoms consists of a thorough history and physical examination, mental status examination, and a laboratory and diagnostic workup to exclude medical causes or depression induced by prescribed or abused substances. Depression is highly treatable and the goal of treatment is full remission. Most cases of depression can be treated with SSRIs and newer antidepressants. Other strategies include switching antidepressants, augmentation, psychotherapy, hospitalization, and ECT. Referral to a psychiatrist may be necessary in refractory, complex, or severe cases.

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Dialogue Box

ADVISORY BOARD

Is the extensive laboratory workup listed recommended for all patients with major depression or just elderly patients with depression?

NEMEROFF

All patients with major depression should have laboratory tests conducted to rule out common medical causes of depression, such as hypothyroidism, B₁₂ deficiency, etc.

ADVISORY BOARD

Antidepressant therapy is clearly indicated for patients who fulfill *DSM-IV* criteria for major depression. What should the clinical threshold be for using it in depressed patients who fail to meet these criteria, such as the patient with dysthymia?

NEMEROFF

There is good evidence that patients with dysthymia respond exceptionally well to treatment with SSRIs. Moreover, patients with so-called sub-syndromal depression (ie, those who have 3 or 4 symptoms of depression) frequently show marked improvement after treatment with antidepressants.

ADVISORY BOARD

Is the clinical use of antidepressant therapy (ie, efficacy, dose, duration of maintenance use) different when used to treat patients with dysthymia?

NEMEROFF

Although there is not a lot of information about this, it appears that there are more similarities than differences in treating dysthymia and depression.

ADVISORY BOARD

Most clinicians would prefer to use an SSRI as their first-line drug for the treatment of depression. In what specific situations would you recommend that one of the newer antidepressants be used instead?

NEMEROFF

Patients who are sensitive to SSRI side effects such as nausea or sexual dysfunction might do better with a new atypical agent such as mirtazapine, nefazodone or bupropion.

ADVISORY BOARD

How “real” a problem is the depression associated with isotretinoin use? Any thoughts regarding mechanism of causation?

NEMEROFF

There is no systematic controlled study that can inform the field as to whether this is a “real” problem or not. Patients prescribed this agent generally have relatively high rates of depression at baseline. Clearly, this question needs to be addressed in a prospective study.

ADVISORY BOARD

What specific measures do you recommend for managing sexual dysfunction developing in the patient treated with an SSRI?

NEMEROFF

There are no controlled studies demonstrating utility of any of the suggested treatments for SSRI-induced sexual dysfunction. Some of the suggested treatments are dose reduction, drug holiday, bupropion, buspirone, yohimbine, methylphenidate, amantadine, cyproheptadine, and sildenafil.



Dialogue Box

ADVISORY BOARD

How do you manage insomnia developing in the patient treated with an SSRI?

NEMEROFF

Dose reduction frequently helps. If pharmacolog-

ic intervention is necessary, nondependence liability sedative hypnotics such as zolpidem may be helpful; alternatively, the addition of trazodone or mirtazapine is often very helpful.