Depression: Diagnosis and Management for the Primary Care Physician

James M. Ferguson, M.D.

Background: Much has been learned in recent years about the diagnosis and treatment of depression, a serious, commonly overlooked psychiatric illness often seen initially by the primary care physician. The objective of this article is to review the diagnosis and treatment of depression in primary care practice.

Method: Relevant articles on depression were identified by a comprehensive MEDLINE search and classified into the following categories: diagnosis and screening, nonpharmacologic therapy, pharmacologic therapy, newer antidepressant agents, and maximizing antidepressant therapy. The importance to primary care practice was considered in determining the significance of each article reviewed.

Results: Because no laboratory tests exist for depression and no biological markers can be measured routinely, the diagnosis of depression must be made with a number of reliable depression scales and questionnaires that can be completed quickly in the primary care setting. The considerable overlap between depressive and anxiety disorders further complicates an accurate diagnosis. Remission (i.e., absence of symptoms) is the ultimate goal of therapy for patients who have depressive symptoms.

Conclusion: Many patients can be treated safely and effectively for depression in the primary care setting with pharmacologic therapy, which, if completely successful, can lead to full remission of the disorder.

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Reprint requests to: James M. Ferguson, M.D., University of Utah School of Medicine, Pharmacology Research Clinic, 448 E. 6400 S., Suite 200, Salt Lake City, UT 84107 (e-mail: jferguson@protocare.com).

Depression, one of the most common disorders in the primary care setting, is a serious mental illness with an estimated lifetime prevalence rate of 17%.[1] Many patients with depression first seek help from their primary care physician, complaining of a variety of somatic symptoms that actually mask a depressive disorder.[2] The primary care physician may administer an unnecessary battery of laboratory and clinical tests before ruling out any somatic illness. Further complicating an accurate diagnosis is the considerable overlap between depressive and anxiety disorders (e.g., panic disorder, social phobia, generalized anxiety disorder [GAD]); anxiety is associated with significant depression in 50% to 70% of cases.[2] Patients may return repeatedly to their primary care physician seeking resolution of their symptoms, but despite these repeated visits, only 50% of patients with depression who are seen in the primary care setting will be accurately diagnosed, and, of these, less than 10% will be appropriately treated.[2]

Depression has a broad spectrum and carries a high cost to both society and individual patients. In 1990, the cost of depression was estimated at $44 billion annually in the United States: $12.4 billion in direct costs and the remainder in morbidity and mortality costs.[3] In addition, nearly 15% of patients who seek help for their depressive illness but are left untreated commit suicide within 1 month of being seen by a physician. Thus, early and accurate diagnosis of depressive disorders is an important part of the primary care physician's evaluation of every patient.

To locate relevant articles on the diagnosis and treatment of depression, I searched MEDLINE using the search terms *primary care*, *depression*, *diagnosis*, and *treatment*. My findings are discussed below.

DIAGNOSIS AND SCREENING

A major depressive episode is characterized by a depressed mood on a daily basis for a minimum of 2 weeks (Table 1)[4]; major depressive disorder (MDD) is defined by 1 or more major depressive episodes.[5] Dysthymic disorder is characterized by mild depressive symptoms that are less severe than MDD and occur for at least a 2-year period.[6] The incidence of depression increases with age, and the disorder is twice as prevalent in women as in men.

Given the high incidence of depression seen in the primary care setting, it is important that all new patients be screened for it just as they would be, for example, for hypertension. Because there are no laboratory tests for depression and no biological markers that can be routinely measured, the diagnosis of depression is made using a number of reliable depression scales and questionnaires that can be completed quickly in the office setting (e.g., Zung Self-Rating Depression Scale,[7] Beck Depression In-

Table 1. DSM-IV Criteria for Major Depressive Episode[a]

A. At least 5 of the following symptoms must be present for a period of at least 2 weeks and represent a change from previous functioning. Symptoms that are clearly due to a general medical condition or mood-incongruent delusions or hallucinations should not be included. Symptoms must be present nearly every day or most of the day, as reported subjectively or observed by others:
   1. Depressed mood (eg, feels sad or empty or appears tearful)
   2. Markedly diminished interest or pleasure in all or almost all activities
   3. Significant weight loss (when not dieting) or weight gain (eg, a change of >5% of body weight in a month), or a decrease or increase in appetite
   4. Insomnia or hypersomnia
   5. Psychomotor agitation or retardation (not merely subjective feelings of restlessness or being slowed down)
   6. Fatigue or loss of energy
   7. Feelings of worthlessness or excessive or inappropriate guilt (may be delusional; not merely self-reproach or guilt about being sick)
   8. Indecisiveness or diminished ability to think or concentrate
   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 (eg, a mixed disturbance resulting from a manic and depressive 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 (eg, an abused substance or medication) or a general medical condition (eg, hypothyroidism)

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

[a]Adapted with permission from the American Psychiatric Association.[4]

Table 2. Screening for Depression in Primary Care: The SAD-A FACES Mnemonic[a]

Target Symptom of Depression	Useful Questions for Screening
Sleep (insomnia/hypersomnia)	Do you have difficulty falling/staying asleep, or do you sleep too much?
Appetite or weight change	Has your appetite or weight changed?
Dysphoria ("bad mood")	Have you been feeling sad or irritable—down in the dumps?
Anhedonia (lack of interest or pleasure; lack of sex drive)	What do you do to enjoy yourself? Has your interest in (golf, tennis, other hobby) changed any?
Fatigue	How is your energy level?
Agitation/retardation	Do you feel restless or slowed down?
Concentration diminished	Are you having trouble concentrating?
Esteem (low)/guilt	Have you been down on yourself recently?
Suicide/thoughts of death	Do you sometimes feel life is not worth living? Do you ever have thoughts about hurting yourself?

[a]Adapted with permission from Montano.[2]

ventory,[8] or Geriatric Depression Scale[9]). Once depression is diagnosed, a 5- to 10-minute questionnaire using the SAD-A FACES mnemonic (Table 2)[2] can help the physician rapidly identify symptoms of depression and assist in determining appropriate treatment.

TREATMENT

The ultimate goal of therapy is to obtain remission (i.e., complete recovery and removal of all symptoms) rather than merely a response to therapy (in which patients improve but still exhibit depressive symptoms). Treatment should encompass methods that rapidly relieve symptoms (e.g., pharmacotherapy) and prevent relapse and recurrence (e.g., nonpharmacologic therapy and/or pharmacotherapy). Advances in the treatment of depression, which include new agents with dual mechanisms of action and a broader spectrum of efficacy across affective and anxiety disorders, make these goals obtainable.[10]

Nonpharmacologic Therapy

The clinical practice guidelines contained in *Depression in Primary Care*[11] recommend that psychotherapy and patient education should be considered when treating patients with MDD. Psychotherapy should be performed by a qualified mental health professional and can take many forms, including cognitive therapy, behavioral therapy, and interpersonal therapy. Cognitive therapy is frequently of value and is directed toward helping patients identify, evaluate, and modify thoughts and attitudes. It is often used in conjunction with behavioral therapy and interpersonal therapy. All of these forms of therapy are similar in nature and have a structured short-term treatment goal related to the current concerns of the patient. The primary care physician can perform a counseling role by providing the patient with support and insight, offering alternative explanations, and making recommendations. The effectiveness of this counseling may be enhanced by using a specific protocol developed by the primary care physician for use in his or her office; a basic protocol is shown in Table 3.[12] In addition, the primary care physician can explain the biochemical nature of depression and reassure the patient that the symptoms are not due to an inherent personality "weakness." Such education is often helpful.

Pharmacologic Therapy

Increased knowledge about the diagnosis and treatment of depression has greatly enhanced the ability of the primary care physician to provide safe and effective pharmacologic therapy. Choices for such therapy include first-generation antidepressant agents (i.e., tricyclic antidepressants [TCAs] and monoamine oxidase inhibitors [MAOIs]), which have a high incidence of side effects, and newer agents, such as selective serotonin reuptake in-

Table 3. Counseling Depressed Patients: Strategies for Primary Care Physicians[a]

Educate and negotiate
Explain the causes, management, and prognosis of depression
Provide details regarding the treatment plan and therapeutic goals
Listen supportively
Provide personal legitimization and reassurance
Neutralize patient's self-critical thoughts/enhance self-esteem
Solve problems
Increase patient's sense of self-efficacy
Encourage patient to evaluate negative thoughts critically and recognize distortions from reality
Facilitate effective coping
Enable patient to recognize and focus on positive aspects of life
Enable patient to participate in pleasurable and rewarding activities
Recommend self-help materials
Follow up with patient

[a]Adapted with permission from Brody et al.[12]

Table 4. Some Commonly Used Older Antidepressant Agents[a]

Agent	Dosage Range, mg/d
TCAs	
Amitriptyline	150–300
Amoxapine	150–450
Clomipramine	100–250
Desipramine	150–300
Imipramine	150–300
MAOIs	
Phenelzine	45–90
Tranylcypromine	30–50
Atypical Drugs	
Maprotiline	150–200
Trazodone	150–400

[a]Data from Reus,[6] Akiskal et al.,[15] Cohen,[16] and Hartman and Watanabe.[17] Abbreviations: MAOI = monoamine oxidase inhibitor, TCA = tricyclic antidepressant.

hibitors (SSRIs) and serotonin-norepinephrine reuptake inhibitors, which have more favorable side effect profiles.

To evaluate the effectiveness of pharmacotherapy, primary care physicians must become familiar with the Hamilton Rating Scale for Depression (HAM-D),[13] which is currently used as the diagnostic measure of this disorder. As stated earlier, full remission and functional recovery, not merely response, should be the goal of therapy. Depression frequently coexists with anxiety, and antidepressant agents are commonly used to treat this comorbid condition. Objective guidelines for remission include maintaining total scores of ≤ 7 on the HAM-D and 7 to 10 on the Hamilton Rating Scale for Anxiety (HAM-A).[14]

First-generation antidepressant agents. The first-generation agents used to treat major depression (Table 4)[6,15–17]—TCAs and MAOIs—are no longer considered the treatments of choice because of the severity of side effects and the potential for fatalities.

TCAs can be fatal if overdosed and have the potential to interact pharmacologically with a wide variety of drugs. Thus, in instances where these side effects are a concern for the patient, the administration of TCAs requires blood drug level monitoring and an awareness of the myriad drugs with a potential for interacting with TCAs. Side effects—dry mouth, constipation, blurred vision, sedation, weight gain, and sexual dysfunction—frequently prevent patients from completing treatment; therefore, patients who are prescribed these agents must be encouraged by the primary care physician to continue with a full course of therapy if remission of symptoms is to be achieved.[16] Physicians may also be tempted to prescribe a subclinical dose of a TCA to minimize side effects; however, suboptimal dosing can also affect antidepressant efficacy.

Adverse reactions are more frequent and more severe with MAOIs than with other antidepressants because of their mechanism of action (most MAOIs are site-directed irreversible inhibitors of MAO). The most common side effect is orthostatic hypotension; other side effects include sedation, palpitations, dizziness, insomnia, constipation, tachycardia, agitation, peripheral edema, sexual dysfunction, weight gain, myoclonus, and muscle cramps. A potentially fatal hypertensive crisis may occur when these drugs are taken with foods containing tyramine (e.g., aged cheese, wine, or cured meats) or sympathomimetic amines (such as nonprescription cold or weight-loss products). Therefore, it is important for the primary care physician to remind the patient at every visit that he or she must avoid or limit intake of certain foods.[16]

Newer antidepressant agents. Several antidepressant agents with more favorable side effect profiles have been developed recently (Table 5).[15–19] SSRIs, which include citalopram, fluoxetine, fluvoxamine, paroxetine, and sertraline, have played a major role in the evolution of antidepressant pharmacotherapy. Among the SSRIs, citalopram is indicated for the treatment of depression and fluvoxamine for obsessive-compulsive disorder. Fluoxetine is indicated for the treatment of depression, obsessive-compulsive disorder, and bulimia nervosa. Paroxe-

Table 5. Commonly Used Newer Antidepressant Agents[a]

Agent	Dosage Range, mg/d
SSRIs	
Citalopram	20–60
Fluoxetine	20–80
Fluvoxamine	100–300
Paroxetine	20–50
Sertraline	50–200
SNRIs	
Venlafaxine extended release	75–225
Atypical drugs	
Bupropion	300–450
Mirtazapine	15–45
Nefazodone	300–600

[a]Data from Akiskal et al.,[15] Cohen,[16] Hartman and Watanabe,[17] Kehoe and Schorr,[18] and Noble and Benfield.[19] Abbreviations: SNRI = serotonin-norepinephrine reuptake inhibitor, SSRI = selective serotonin reuptake inhibitor.

tine is indicated for the treatment of depression, obsessive-compulsive disorder, panic disorder, and social anxiety disorder. Sertraline is indicated for the treatment of depression, obsessive-compulsive disorder, panic disorder with or without agoraphobia, and posttraumatic stress disorder.

Drugs in this class are better tolerated than either TCAs or MAOIs, have no cardiac liability, are less sedating, and do not cause weight gain. Adverse events include nausea, headache, lack of coordination, sleep disturbance, sexual dysfunction, and tremor. Nausea usually resolves with therapy, but can be minimized by reducing the dosage or taking the drug with food.[16]

SSRIs can usually be taken once a day, which is a significant advantage over older agents. However, they may have a time to onset of action as long as 5 weeks.[6,15] The choice of SSRI agent is based on differences in half-life and variance in the risk of drug-drug interactions, with the majority of drug-drug interactions resulting from inhibition of cytochrome P450 enzymes. This interaction impedes the metabolism of many drugs and may potentially enhance adverse reactions to any of the drugs involved.[16] For this reason, patients taking multiple medications should be monitored closely.[16]

Venlafaxine extended release (XR) is the only antidepressant that inhibits reuptake of both serotonin and norepinephrine; it also weakly inhibits dopamine reuptake. Data suggest that agents with both serotonergic and noradrenergic neurochemical effects may provide a viable treatment option for patients with concomitant anxiety and depression.[20,21] Because anxiety and depression frequently coexist, this information should be considered when choosing medication. Venlafaxine XR is indicated for both depression and GAD.[22] Venlafaxine has a strong affinity for the imipramine receptor, resulting in an antidepressant effect similar to that produced by TCAs. However, it does not inhibit MAO or antagonize cholinergic, histaminergic, or α-adrenergic receptors, which accounts for its relatively favorable adverse event profile. The most common adverse event is nausea; other adverse events include nervousness, dry mouth, constipation, fatigue, anorexia, somnolence, insomnia, dizziness, abnormal ejaculation, and headache. Most adverse events associated with venlafaxine are mild to moderate, occur early in the course of treatment, and resolve with continued therapy. Starting therapy at lower dosages and gradually titrating upward can minimize nausea, the most common side effect; nausea also diminishes with time after the maintenance dosage has been reached.[16,23,24]

Studies have shown that a response to venlafaxine can occur as early as week 1.[23] As the result of a positive dose-response curve, increasing the dosage has been shown to increase rates of response and remission.[15] Venlafaxine has a low protein-binding capability (~30%) and demonstrates only limited inhibition of cytochrome P450 enzymes, which decreases the likelihood of drug-drug interactions.[25,26] The rank order of potency for inhibition of cytochrome P450 among frequently prescribed antidepressants is as follows: paroxetine > fluoxetine > sertraline > fluvoxamine > clomipramine > venlafaxine.[25]

In a recent meta-analysis[27] comparing venlafaxine XR and SSRIs, venlafaxine XR produced significantly higher remission rates (i.e., absence of symptoms) than SSRIs after 8 weeks of treatment for depression (45% vs. 35%). When venlafaxine XR was compared with fluoxetine in depressed outpatients, 37% of venlafaxine-treated patients achieved full remission (HAM-D score ≤ 7) at 8 weeks, compared with 22% of fluoxetine-treated patients. Both drugs were well tolerated, with nausea and dizziness being the most commonly reported adverse events for venlafaxine and nausea and diarrhea the most common adverse events for fluoxetine.[28]

Nefazodone is an analog of trazodone. It is an antagonist of the postsynaptic serotonin receptor and the presynaptic serotonergic reuptake protein. Comparative studies have shown that nefazodone has an efficacy profile similar to that of imipramine. It also has a short half-life, requiring that it be dosed twice daily. It inhibits cytochrome P450 3A4 (CYP3A4) and therefore significantly enhances sedation, cognition impairment, and "hangover" symptoms when administered with alprazolam, triazolam, or midazolam. It also should not be given concomitantly with terfenadine or cisapride, because inhibition of CYP3A4 leads to high plasma levels of these agents, which can in turn lead to fatal ventricular arrhythmias after QT prolongation.[16] Common side effects include somnolence, dry mouth, nausea, and dizziness.[29]

Bupropion is thought to exert its antidepressant activity through inhibition of norepinephrine reuptake.[30] It is a clinically effective antidepressant, but its use in the primary care setting had been limited because of its potential for inducing seizures at higher doses. The development of a sustained-release form of bupropion offered a better-tolerated formulation with a lower risk of seizures.[31] Combination therapy with bupropion and an SSRI is currently being used to treat patients with treatment-resistant depression and SSRI-induced sexual dysfunction.[32] Common adverse events associated with bupropion treatment are agitation, anxiety, insomnia, dry mouth, nausea, constipation, and tremor.[16]

Mirtazapine is an antagonist of the presynaptic α_2-adrenoceptor and the postsynaptic serotonin-2 and -3 receptors.[18] Mirtazapine has been shown to be more effective than trazodone and as effective as amitriptyline in treating patients with moderate to severe depression.[16,18] The sedative effect of mirtazapine is comparable to that seen with amitriptyline, but weight gain has been reported more frequently. Mirtazapine is metabolized by several cytochrome P450 enzymes, so the potential for clinically important drug-drug interactions exists.[16,18]

Table 6. Patients Who Should Be Considered for Referral to a Psychiatrist

Patients with symptoms of greater severity
Suicidal tendencies/history of suicide attempts
Severe depression
Bipolar disorder
Atypical depression
Psychotic depression
Patients who have experienced drug-drug interactions
Patients who are treatment resistant

MAXIMIZING ANTIDEPRESSANT THERAPY

With appropriate treatment, depressed patients have an excellent probability of attaining remission (i.e., recovering and becoming virtually asymptomatic). To ensure that patients attain remission and have a low risk of relapse and recurrence, pharmacotherapy should be maintained at the maximum tolerated dosage for at least 4 to 9 months. Thereafter, long-term maintenance therapy should be instituted to prevent the development of a new episode. The length of the maintenance phase varies by patient, but generally such therapy should continue for an additional 4 to 5 months.[14] During this long-term maintenance phase, it is important to continue monitoring the patient for adverse events.

If a patient responds partially but not fully to a given therapy, a dosage adjustment should be considered. However, if there is no response at 6 weeks or only a partial response at 12 weeks, then alternative therapy is indicated.[33] An agent with a different mechanism of action may produce an effect in some nonresponders or partial responders. In cases of refractory depression, augmentation therapy with lithium may be warranted,[6] and those patients should be referred to a psychiatrist[2] (Table 6).

CONCLUSION

Each year, a significant number of patients with depression, or more commonly, depression associated with an anxiety disorder, will be seen by a primary care physician. Patients can be diagnosed rapidly with any one of several reliable questionnaires that can be administered in the office. These questionnaires should become a routine part of the primary care physician's practice, much like blood pressure monitoring. Once a diagnosis of a depressive disorder has been established, a differential diagnosis can be made to determine the primary disorder and select the appropriate therapy, which may include both nonpharmacologic and pharmacologic treatments. Some newer pharmacologic agents enable a treatment goal of remission and a return to wellness. Agents with a dual mechanism of action and well-documented comparative studies demonstrating an ability to attain remission may be particularly effective in achieving the goal of recovery. An understanding of the risk-benefit profiles, adverse events, drug-drug interactions, and onset of action of these antidepressant agents is critical for appropriate management of depressed patients.

Drug names: alprazolam (Xanax and others), amitriptyline (Elavil and others), amoxapine (Asendin and others), bupropion (Wellbutrin), cisapride (Propulsid), citalopram (Celexa), clomipramine (Anafranil and others), desipramine (Norpramin and others), fluoxetine (Prozac), fluvoxamine (Luvox), lithium (Eskalith and others), midazolam (Versed), mirtazapine (Remeron), nefazodone (Serzone), paroxetine (Paxil), phenelzine (Nardil), sertraline (Zoloft), tranylcypromine (Parnate), trazodone (Desyrel and others), triazolam (Halcion), venlafaxine (Effexor).

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