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Depression

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Depression: Meeting the clinical challenge

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ABSTRACT Major depression is one of the most common illnesses that primary care physicians are called on to diagnose and treat. Patients with major depression have high medical costs, many unexplained physical symptoms, and as much social and vocational disability as persons with most chronic medical illnesses. Selective serotonin reuptake inhibitors are the usual first-line treatment, ideally in combination with psychotherapy. Appropriate management of depression improves the daily functioning and overall health of affected persons.

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Depression is a common illness that affects almost 18 million people in the United States each year.[1] It is second only to hypertension as the most frequent chronic condition encountered in general medical practice.[2] Roughly 13% of men and 21% of women experience an episode of major depression during their lifetime,[3] and more than half of those affected have recurrent episodes. Depression is increasingly seen in younger people, with a median age of onset in the late 20s.[4] In most patients with depression, the disease takes a relapsing/remitting course; in 10%-20% of patients, the disease is chronic, much like asthma.[5] Episodes last a mean of 6 months but often persist for 1 year or longer.[6] The risk of relapse is 50% after one episode of major depression and 80% after two episodes.[7] The latter qualifies for the diagnosis of recurrent major depression. Between episodes, a normal level of functioning usually returns, but 20%-35% of patients have persistent residual symptoms that impair social or occupational pursuits.[6]

The toll taken by depression is enormous. Major depression accounts for $6,000 in health- and work-related expenditures per worker per year.[8] In a 4-year study, depressed older adults were significantly more likely to die of cardiac disease during follow-up than their nondepressed counterparts.[9] Even after accounting for the effects of physical illness, depressed older adults have a significantly higher 4-year mortality rate.[10]

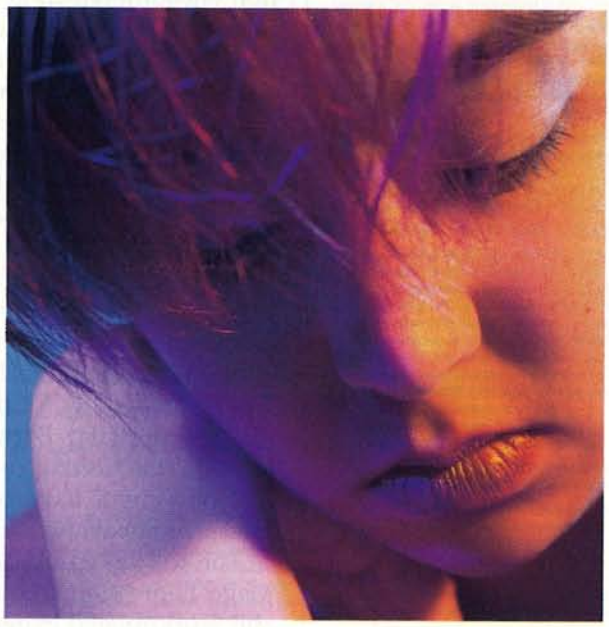
According to one large survey, fewer than 35% of adults in the United States with a depressive or anxiety disorder are treated appropriately.[11] Three fourths of those who received poor-quality care had seen a health care professional during the 1-year period when the disorder occurred.[11] African-Americans are significantly

less likely to receive proper care, an ethnic disparity similar to that found in a variety of other medical conditions.[12]

Primary care providers bear the burden of recognizing depression in patients who are not seeking psychological treatment. Physicians should be prepared to provide aggressive initial treatment with antidepressant medications that offer robust efficacy and the best chance for full remission.

Diagnosis: Basics and challenges

• *History* features that indicate increased risk for depression include a family or personal history of depression, multiple medical problems, unexplained physical symptoms, chronic pain, and frequent use of medical services.[13] Psychosocial stressors that often precede a major depressive episode include the death of a loved one, marital separation, or the ending of an important relationship. It is particularly important to recognize a family problem, since this is an ongoing stressor that may hamper the patient's response to treatment.



The *Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition (DSM-IV)* criteria for major depression include depressed mood or loss of interest in nearly all activities for at least 2 weeks, along with at least four of the following symptoms: insomnia or hypersomnia, feelings of worthlessness or excessive guilt, fatigue or loss of energy, diminished ability to think or concentrate, substantial change in appetite or weight, psychomotor agitation or retardation, and recurrent thoughts of death or suicide.[14]

The level of illness can range from mild to severe, but the symptoms must cause clinically significant distress or impair social, occupational, or other important areas of functioning. Symptoms cannot be due to the direct physiologic effects of a substance (such as a medication or drug of abuse) or a general medical condition (such as hypothyroidism). And the symptoms cannot be better accounted for by bereavement.

• *Subtypes and related disorders* Depression with melancholic features is defined by anhedonia or a depressed mood that does not improve, even temporarily, when something good happens. At least three of the following symptoms must also be present: depression that is worse in the morning, early morning awakening, psychomotor retardation or agitation, significant anorexia or weight loss, and excessive or inappropriate guilt. Melancholic features are important to recognize, because affected patients do not respond to psychotherapy alone and usually require drug treatment.

Depression with atypical features is defined by mood reactivity, or the ability to cheer up in response to positive events, and at least two of the following: significant weight gain or increased appetite, hypersomnia, a leaden feeling in arms or legs (leaden paralysis), and a long-standing sensitivity to perceived interpersonal rejection. This form of depression has an earlier age of onset (late teens to late 20s) compared with the melancholic form (late 30s to late 40s). Despite the appellation, atypical depression is frequently encountered in outpatient practice.

Major depression may be accompanied by psychotic features such as hallucinations or delusions that are either congruent or noncongruent with the depressive mood. These features are a crucial specifier in predicting treatment response. Fewer than 30% of these patients respond to an antidepressant or antipsychotic agent alone,[15] but 60%-70% benefit from a combination of the two classes of drugs, and more than 90% respond to electroconvulsive therapy (ECT).[15]

Postpartum depression, which occurs within 4 weeks of giving birth, is marked by a fluctuating course and mood lability. The common, so-called baby blues can last 3-5 days after delivery and usually resolve spontaneously. Major postpartum depression, with the accompanying danger of psychotic episodes and infanticide, is rare and characterized by marked insomnia, anxiety, and lack of interest in the infant. This severe form is more common in women with a history of a mood disorder or previous postpartum depression.

Dysthymic disorder is a low-grade chronic depressive disorder characterized by at least 2 years of depressed mood most of the time plus at least two of the following symptoms: poor appetite or overeating, insomnia or hypersomnia, fatigue or low energy, low self-esteem, indecisiveness or poor concentration, and feelings of hopelessness. Dysthymic disorder may precede major depression in up to 25% of clinical cases.

It is important to distinguish major unipolar depression from bipolar disorder (both manic and depressive episodes). A family history of bipolar depression or acute psychosis may increase risk for bipolar disorder. Treatment with antidepressants often causes hypomania or mania in patients with bipolar disease.[16]

Since depression is a clinical diagnosis, laboratory testing is usually unnecessary. But serum levels of thyroid-stimulating hormone should be measured in women older than 65 and in persons with signs or symptoms of hypothyroidism.

• *Comorbid conditions* Depressive episodes are frequently associated with substance abuse or dependence on sedatives such as alcohol or stimulants such as cocaine.

Depression is also closely linked to anxiety, particularly generalized anxiety disorder. Up to 95% of depressed persons experience symptoms of anxiety, and some 58% fulfill the criteria for both major depressive disorder and anxiety disorder.[17] Some research has indicated that primary care practitioners tend to underdiagnose depression and overdiagnose anxiety.[18] In one study, depression was treated more often with anxiolytic agents than antidepresssants, and only 13% of depressed patients received appropriate antidepressant therapy.[18]

Other comorbidities include schizophrenia, anemia, hyperthyroidism, hypothyroidism, cancer, chronic illnesses, and central nervous system disease. People with a chronic medical illness are almost twice as likely as the general population to suffer from depressive disorders.[19] About 20% of patients who have had an acute myocardial infarction (MI) have major depression.[20]

• *Suicide assessment* should be done both initially and throughout the course of treatment. Initial evaluation must include specific questions, such as "Do you ever think of hurting yourself or taking your own life?" An affirmative response should be followed by "Do you currently have a plan?" and if yes, "What is your plan?"[21] Unfortunately and despite such precautions, some depressed persons are likely to die by suicide. Risk is influenced by the nature of the physician-patient alliance, social supports, access to and lethality of means of suicide, and history of suicidal behavior. Depressed men are more likely than depressed women to commit suicide, and elderly white men are at highest risk.[22]

Primary care providers bear the burden of recognizing depression in patients who are not seeking psychological treatment.

• *Hospitalization* should be considered for patients who are at risk for suicide or homicide, who lack psychosocial supports, and who are unable to adequately care for themselves, cooperate with outpatient treatment, or provide reliable feedback to the physician regarding their clinical status. Recovery from major depression is enhanced by an environment that encourages safety, constructive activity, positive interpersonal interactions, and compliance with treatment. If the environment lacks these features or exposes the patient to undesir-

Table 1

Common antidepressant medications

Drug	Starting dose	Maximum dose	Comments
SSRIs			SSRIs are considered first-line therapy for previously untreated patients; titrate doses slowly to minimize side effects such as nausea, headache, insomnia, nervousness or agitation, and sexual dysfunction; avoid concurrent use with MAOIs; fluoxetine, fluvoxamine, and sertraline should not be combined with diazepam (Valium) or phenytoin (Dilantin)
Citalopram HBr (Celexa)	20 mg qd	40-60 mg/d	
Fluoxetine HCl (Prozac)	20 mg/d am	80 mg/d	
Fluvoxamine maleate (Luvox)	50 mg bedtime	100-300 mg/d	
Paroxetine HCl (Paxil)	20 mg/d am	50 mg/d	
Sertraline HCl (Zoloft)	50 mg qd	200 mg/d	
TCAs			TCAs may benefit patients with comorbid anxiety; common side effects include dry mouth, constipation, urinary hesitancy, blurred vision, confusion, and weight gain
Amitriptyline HCl (Elavil)	75 mg/d, in divided doses	150 mg/d	
Desipramine HCl (Norpramin)	100-200 mg/d	300 mg/d	
Imipramine HCl (Tofranil)	75 mg/d	150 mg/d	
Nortriptyline HCl (Aventyl, Pamelor)	15 mg tid or qid		
MAOIs			Dietary and medication restrictions necessary; side effects include hypertensive crisis, serotonin syndrome, dizziness, orthostatic hypotension, weight gain, and sexual dysfunction
Phenelzine sulfate (Nardil)	15 mg tid	60-90 mg/d	
Tranylcypromine sulfate (Parnate)	30 mg/d, in divided doses	60 mg/d	
Atypical agents			Sexual dysfunction relatively uncommon with bupropion, nefazodone, and mirtazapine; bupropion should not be prescribed for patients with a seizure disorder or active eating disorder; common side effects of bupropion are anxiety, agitation, and insomnia; mirtazapine side effects include transient somnolence, weight gain, dizziness, dry mouth, and constipation; nefazodone side effects include nausea, dizziness, insomnia, asthenia, and agitation; side-effect profile of venlafaxine is identical to that of SSRIs
Bupropion HCl (Wellbutrin)	100 mg bid	100 mg tid	
Mirtazapine (Remeron)	15 mg/d qd	45 mg/d	
Nefazodone HCl (Serzone)	100 mg bid	600 mg/d	
Venlafaxine HCl (Effexor)	75 mg/d am	225 mg/d	

Key: MAOI = monomine oxidase inhibitor; SSRI = selective serotonin reuptake inhibitor; TCA = tricyclic antidepressant.

able or dangerous activities (such as alcohol or drug abuse), hospitalization or an intensive day care program should be considered. Psychosis may also warrant hospitalization.

• *Referral to a psychiatrist* Primary care clinicians can provide effective therapy for more than 75% of patients with depression.[23] Psychiatric consultation is recommended for patients with a history of mania or psychosis and for those who have not responded to two different medications.

The therapeutic approach

The goal of treating depression is to reduce morbidity and improve the patient's quality of life. Treatment begins with the development of a trusting therapeutic alliance with the patient and possibly with the family as well.

• *Antidepressant drugs* have become the first-line treatment in both primary and specialty care settings (Table 1). In the past 10 years, eight new drugs have been approved: bupropion HCl (Well-

butrin), fluoxetine HCl (Prozac, Serafem), sertraline HCl (Zoloft), paroxetine HCl (Paxil), venlafaxine HCl (Effexor), nefazodone HCl (Serzone), mirtazapine (Remeron), and citalopram HBr (Celexa). Reboxetine (Vestra) is expected to be approved soon. While not sanctioned for the treatment of depression, fluvoxamine maleate (Luvox) also appears to be an effective antidepressant.[24]

Some 60%-70% of patients respond to currently available agents.[25] No single drug has proved to be more effective than another,[25] and no single drug can be recommended as optimal because of the heterogeneity of patients. Factors to consider include previous response of the patient or family members to a medication, drug-drug interactions, side effects, patient preference and age, costs, and comorbidities.

• *Patients with comorbidities* Providers must treat depression aggressively in persons with other medical problems, such as cardiovascular disease, to reduce the risk for somatic distress and consequent poorer self-care, which in turn worsens the cardiovascular prognosis.[9] Major depression in patients hospitalized with an MI is associated with a two to four times increased risk for cardiac mortality.[26] Physicians can explain that effective relief of depression often makes chronic illness and physical symptoms more bearable.

• *Treatment phases* Depression is a chronic condition, and treatment consists of acute, continuation, and maintenance (or prophylaxis) phases. In the acute phase (6-12 weeks), the aim is a remission of depressive symptoms. Patients who show significant improvement should continue pharmacotherapy for at least 6 months.[27] The highest risk of relapse is during this continuation phase (16-20 weeks). Psychotherapy at this time helps attenuate stress and other conflicts that might prompt a new depressive episode.

Long-term, if not lifelong, maintenance treatment should be strongly encouraged for patients with a history of two or more episodes of major depression, as well as for those who have more severe or psychotic episodes, an incomplete response to treatment, or an increased suicide risk.[28] A 2-year course of maintenance drug therapy has been shown to markedly decrease risk of recurrence.[29] Patients should generally be seen every 4-12 weeks during the first year of maintenance therapy and at 6-month to yearly intervals thereafter.

SSRIs: Benefits and caveats

A full understanding of the biologic basis of depression remains elusive, but the most consistent findings point to low serotonergic function.[30] Selective serotonin reuptake inhibitors (SSRIs) are potent, relatively selective inhibitors of serotonin reuptake at presynaptic terminals, and are the usual first choice for previously untreated patients. The most common adverse effects are nausea, headache, insomnia, nervousness or agitation, and sexual dysfunction. Rare side effects include extrapyramidal symptoms such as akathisia, lactation, and lowered seizure threshold. Overdoses are rarely fatal.

One notable difference among the SSRIs is in half-life. Agents with a longer half-life provide greater protection against the effects of noncompliance, postdiscontinuation relapse, and abrupt withdrawal symptoms. But such medications also require more vigilance for drug-drug interactions following discontinuation. Fluoxetine has the longest half-life: 2-3 days for the parent compound and 7-9 days for its active metabolite. A weekly enteric-coated fluoxetine preparation is also available for continuation treatment. Doses should be adjusted gradually to minimize adverse effects and enhance the likelihood of long-term adherence.

• *Sexual dysfunction,* seen in nearly 60% of patients, is often the most difficult side effect to manage.[31] It causes distress, impairs quality of life, and contributes to noncompliance. The clinician must ask about the patient's current sexual function and satisfaction before therapy begins, not only to assess a common symptom of depression but also to provide a baseline against which to compare persistent or new-onset complaints. Sexual function must also be specifically addressed during the course of treatment. One study found that the reported incidence of sexual dysfunction was 50% when patients were asked about it and only 10% when clinicians relied on patients to mention it.[31]

Sexual dysfunction is often dose-related and may begin early or late in the course of treatment. Men may report erectile or ejaculatory dysfunc-

tion, and both men and women may experience loss of libido or anorgasmia. Sometimes, but not always, the dysfunction resolves over time. Sexual problems are most common with SSRIs and least common with bupropion, nefazodone, mirtazapine, and tricyclic antidepressants (TCAs) other than clomipramine HCl (Anafranil).

General management strategies include waiting for the dysfunction to diminish over time (if it is mild or intermittent), reducing the antidepressant dose to a minimally effective level, giving pharmacologic antidotes, or switching to another antidepressant.

• *SSRI drug interactions* The most serious adverse pharmacodynamic interaction is the central serotonin syndrome.[32] The best-known and most serious cause is giving an SSRI in combination with a monoamine oxidase inhibitor (MAOI). SSRIs inhibit cytochrome P-450 isoenzymes, and the cytochrome P2C6 (CYP2C6) isoenzyme—which is inhibited by fluoxetine, sertraline, and fluvoxamine—metabolizes phenytoin (Dilantin) and diazepam (Valium). Little data support lethal drug interactions, however.

Spending time to provide support and education and to establish a collaborative relationship with the patient can improve adherence and outcome.

• *The discontinuation syndrome* Patients must be carefully monitored for the recurrence of depression after a medication is discontinued. Doses should be tapered slowly over a 4-week period to avoid a discontinuation syndrome, which is associated with flu-like symptoms or malaise, dizziness, gastrointestinal disturbances, paresthesias, and changes in mood, affect, appetite, and sleep.[33] Discontinuation symptoms appear to stabilize if the original antidepressant is reintroduced.

Other effective antidepressant medications

• *Bupropion* has proven efficacy, but it must be taken in divided doses, has a potentially activating side-effect profile, and carries a slightly increased risk (1/10,000) for grand mal seizure. This agent should not be given to patients with a history of seizures or with an active eating disorder. The main advantage of bupropion is the reduced risk of sexual dysfunction. The most common side effects are anxiety, agitation, and insomnia.

• *TCAs* benefit patients with comorbid anxiety. Anticholinergic side effects include dry mouth, constipation, urinary hesitancy, blurred vision, increased intraocular pressure, and confusion. Orthostatic hypotension can occur. Prolongation of the QT interval and interaction with class 1 antiarrhythmic agents are potentially serious adverse events. Other important side effects are sweet craving and weight gain and the exacerbation of narrow-angle glaucoma (in susceptible patients). Overdose is lethal with a 10-day supply of 200 mg/d. Blood levels can be monitored for nortriptyline HCl (Aventyl, Pamelor), desipramine HCl (Norpramin), and imipramine HCl (Tofranil). But the less-than-optimal side-effect profile of TCAs is associated with an unacceptable incidence of noncompliance.

• *MAOIs* Anecdotally and in many uncontrolled trials, many patients who do not respond to the newer antidepressants show a clear response to the MAOIs, phenelzine sulfate (Nardil) or tranylcypromine sulfate (Parnate).[34] Depression with atypical features and depression associated with marked interpersonal sensitivity are two of the strongest indications for MAOI therapy.[35]

Salient caveats of treatment with these agents involve dietary prohibitions (eliminating high-tyramine foods) and drug-drug interactions that place patients at risk for a hypertensive crisis or the serotonin syndrome. The latter is characterized by fever, muscular rigidity, hypotension, convulsions, and coma. Other side effects include dizziness, orthostatic hypotension, weight gain, and sexual dysfunction.

• *Venlafaxine* is the first of a new class of antidepressants, the serotonin norepinephrine reuptake inhibitors. The side-effect profile is identical to that of the SSRIs. At higher doses, venlafaxine can

cause hypertension, so the patient's blood pressure should be monitored.

• *Nefazodone* is a serotonergic drug that blocks reuptake in addition to other, more complex serotonergic effects. It is structurally similar to trazodone HCl (Desyrel) and may benefit patients with comorbid anxiety. A lower incidence of sexual dysfunction makes nefazodone a welcome alternative for patients who complain of this side effect with an SSRI or venlafaxine. Since nefazodone inhibits CYP3A4, doses of alprazolam (Xanax) and other drugs cleared by this isoenzyme should be reduced.

• *Mirtazapine* was the first noradrenergic and specific serotonergic antidepressant marketed in the United States. This agent enhances the release of 5-hydroxytryptamine (5-HT) by directly blocking 5-HT2 and 5-HT3 receptors, which may account for its anxiolytic and sleep-improving properties as well as its lack of adverse events compared with SSRIs.[36] The most common side effects are transient somnolence (in more than 50% of patients), increased appetite and weight gain, dizziness, dry mouth, and constipation.[37] Mirtazapine carries a slight risk of agranulocytosis. An orally disintegrating antidepressant form (Remeron SolTab) is now available in the United States.

Managing treatment-resistant depression

Approximately 29%-46% of patients respond only partially or not at all to antidepressants.[38] Many clinicians add a second medication for treatment-resistant patients. Augmentation with stimulants is reportedly useful in withdrawn, anergic, or apathetic patients.[39] Lithium (Eskalith, Lithonate, Lithotabs, etc.) is the best-established strategy, with seven of nine placebo-controlled trials in treatment-resistant patients reporting positive results.[40] Buspirone (BuSpar) and bupropion augmentation have also been shown to be beneficial.[41,42] And four of five placebo-controlled studies found that augmenting an SSRI with pindolol was more rapidly effective than an SSRI plus placebo.[43]

Compliance and education

Spending time to provide support and education and to establish a collaborative relationship with the patient can improve adherence and outcome.[44] It is also helpful to educate family members about the nature of the illness and try to enlist their support and cooperation. Noncompliance is often difficult to predict. Nearly half of all outpatients who receive an initial antidepressant prescription stop taking it during the first month of therapy, with intolerance as a frequent cause of discontinuation or nonresponse.[38] Further, few patients receive the recommended level of monitoring.[45] Close vigilance during treatment is crucial, and telephone follow-up is often helpful.[46]

When to consider ECT

ECT has the highest rate of response of any form of therapy and should be considered for virtually all patients with moderate or severe major depression who have not responded to pharmacologic interventions. The best-documented indications are psychotic depression and depression with catatonic stupor.[4] There are no absolute contraindications to ECT. Depressive symptoms improve relatively quickly, and the safety profile is excellent. The chief side effect, impaired cognition, can be minimized with unilateral therapy.

Psychotherapeutic interventions

In general, most patients should be managed with both medications and psychotherapy. The latter helps the patient reverse the negative self-estimations and feelings about the future that are such ubiquitous features of depression. An ongoing therapeutic relationship may help the patient maintain therapeutic gains and, in selected cases, delay or prevent relapse.

Psychotherapy also educates the patient and family about the psychology and biology of major depression. It helps them understand that medications must be taken daily, that it may take up to 6 weeks for a noticeable effect, and that the medication must be taken even after the patient is feeling better. Patients and family members should be encouraged to call to resolve questions.

Conclusion

Depression causes more functional impairment than diabetes mellitus, arthritis, hypertension, back problems, and gastrointestinal disorders. Other

mental disorders, including alcohol or substance abuse and dependence, and general medical comorbidities must be assessed and treated appropriately. The presence and degree of suicidality is important in the choice and intensity of treatment throughout the course of the disorder. Effective treatments include antidepressants, psychotherapy, and ECT. Patients benefit most from a combination of drug therapy and psychotherapy. ■

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SELF-EXAMINATION

1. Which of the following statements about depression is false?
   a) More than 50% of patients have recurrent episodes.
   b) The median age of onset is the late 20s.
   c) About 15% of patients have a chronic course.
   d) The risk of relapse is 50% after two episodes of major depression.
   e) About 35% of Americans with depression are treated appropriately.

2. Which of the following is not a diagnostic criterion for major depression?
   a) depressed mood for 1 week
   b) loss of interest in almost all activities for 2 weeks
   c) fatigue
   d) weight loss
   e) disordered sleep

3. Most persons who have major depression with psychotic features benefit from electroconvulsive therapy.
   a) true
   b) false

4. All of the following medications except _____ are associated with a lower incidence of sexual dysfunction.
   a) bupropion
   b) nefazodone
   c) fluoxetine
   d) desipramine
   e) mirtazapine

5. Which of the following side effects is not associated with the stated medication?
   a) headache with citalopram
   b) seizure with bupropion
   c) confusion with mirtazapine
   d) hypertension with venlafaxine
   e) blurred vision with amitriptyline

Answers at end of reference list.

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Answers: 1)d, 2)a, 3)a, 4)c, 5)c