CME CREDIT

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Diagnosing and treating depression in primary care patients: Looking beyond physical complaints

ABSTRACT

Depression is common, but often overlooked because patients with depression often present with somatic complaints rather than psychological ones. Primary care physicians must learn to recognize depression and be thoroughly familiar with its treatment, because this disease is common and serious.

KEY POINTS

Up to 20% of patients seen in a primary care office may meet the criteria of a mood disorder.

Depression in the primary care setting should not be a diagnosis of exclusion. When diagnosing depressive disorders, physicians should pay particular attention to the character and duration of symptoms.

Depression may be secondary to alcohol or drug abuse, and remits rapidly when the offending substance is eliminated.

All antidepressant drugs are approximately equally effective, but certain considerations—age, previous response to a particular drug, side effect profile, concurrent nonmood psychiatric disorders, interactions, need for serum level monitoring, risk of overdose, and cost—make the selection process more rational than arbitrary.

ALTHOUGH NEW DRUGS have revolutionized the treatment of depression, this disorder remains a major challenge to the primary care physician. Depression is one of the most common conditions in the primary care office. Yet the signs and symptoms are not straightforward, are often masked by complaints of physical problems, and often coexist with other medical problems.

In this guide for the primary care physician, we outline some tips for identifying depression in different age groups, present our approach to initiating treatment, and provide some advice for following patients after treatment has begun.

DEPRESSION IS COMMON

The prevalence of mental illness in patients who present to primary care physicians is remarkably high. Up to 70% have psychological or psychiatric complaints,[1] with mood disorders among the most common.[2] Community samples find that from 2% to 9% of patients meet the full criteria for diagnosis of a mood disorder according to the *Diagnostic and Statistical Manual of Mental Disorders*, 4th edition (DSM-IV),[3] and approximately 13% have a "subthreshold" diagnosis; although they have fewer symptoms, these patients have considerable impairment of quality of life and would benefit from monitoring and treatment.[4,5]

The prevalence of major depression in the general population ranges from 4% to 9%. Depression affects as many as 10% of men and 20% of women at some point in their lives,[6] and an estimated 2.5% of men and 8% of women at any given time.

TABLE 1

Diagnostic criteria for major depression and dysthymic disorder

Major depressive disorder

Five of the following symptoms must be present for at least 2 weeks, nearly every day. At least one of the first two criteria must be present:

- Depressed mood
- Loss of interest or pleasure
- Loss of appetite or weight
- Insomnia or hypersomnia
- Psychomotor retardation or agitation
- Fatigue or loss of energy
- Feelings of worthlessness or guilt
- Diminished ability to think or concentrate
- Recurrent thoughts of death or suicide

Dysthymic disorders

Chronic depressed mood more often than not, lasting for at least 2 years. The symptoms are not as severe or disabling as a major depressive disorder and include two or more of the following features:

- Poor appetite or overeating
- Insomnia or hypersomnia
- Low energy or fatigue
- Low self-esteem
- Poor concentration or difficulty making decisions
- Feelings of hopelessness

SOURCE: DIAGNOSTIC AND STATISTICAL MANUAL OF MENTAL DISORDERS, 4TH EDITION

Consider depression early in the course of new unexplained somatic complaints

DEPRESSION IS SERIOUS

In the 15 months after the depression is diagnosed, mortality rates in affected patients are four times higher than in age-matched controls.[6]

Depression is also costly, second only to cardiovascular disease in the time lost from work and lost productivity that it causes.[7] By one estimate,[8] depression costs society $44 billion per year, of which 72% consists of indirect costs—loss of productivity and absenteeism (55%) and loss of earnings due to suicide (17%). The direct costs of treatment account for only 28.4%, and antidepressant medication costs account only for 2%. These findings strongly support the economic benefit of detecting and treating depression.

DEPRESSION IS OFTEN OVERLOOKED

Primary care physicians recognize mood disorders in only 25% to 50% of affected patients and miss the diagnosis of major depressive disorder in up to 66%.[9] One reason is that patients typically present with physical symptoms such as fatigue, headache, and insomnia rather than a depressed mood.[10] One study[11] found an organic cause of these symptoms in only 16% of outpatient cases, with treatment often ineffective. Therefore, it is important to consider depression early in the course of new unexplained somatic complaints.

NOT A DIAGNOSIS BY EXCLUSION

Depression in the primary care setting should not be a diagnosis of exclusion. Several clues, such as frequent primary care visits for unexplained symptoms, one or more pain complaints, or a recent stressful life event, should prompt an early, more thorough search for the presence of the formal diagnostic criteria for mood disorders (TABLE 1).[1,3] When diagnosing depressive disorders, physicians should pay particular attention to the character and duration of symptoms. A dysphoric or depressed mood lasting more than 2 weeks and accompanied by neurovegetative and psychological symptoms is a tip-off (TABLE 1), especially when social and occupational functioning is diminished.

In screening for depression, primary care physicians can use a questionnaire such as the General Health Questionnaire (GHQ),[12] the Zung Self-Rating Depression Scale (ZSRDS),[13] the Center for Epidemiological Studies-Depression Scale,[14] or the Beck Depression Inventory,[15] or use a rating scale such as the Primary Care Evaluation of Mental Disorders.[2]

If the patient meets DSM-IV criteria for a depressive disorder, the primary care physician should rule out alcohol or drug abuse. Depression may be secondary to these prob-

TABLE 2

Atypical presentations of depression in older adults

- Accidental overdose
- Alcohol or substance abuse
- Anorexia, weight loss
- Anxiety disorders
- Incontinence
- Loneliness, social withdrawal
- Marital discord
- Obsessions and compulsions
- Other behavioral disturbances
- Paranoid states
- Physical disorders and pain
- Pseudodementia
- Screaming
- Unlawful behaviors (shoplifting, inappropriate sexual acts)

lems and remits rapidly when the offending substance is eliminated.

Diagnosing depression in older patients

Do not assume that all depressive symptoms are due to the medical illness

Although the risk factors for depression are the same in older patients as in younger ones, the symptoms may differ. Young adults more often present with subjective dysphoria (a sad, "blue" feeling or loss of interest or pleasure), whereas older patients are more likely to have:

- Vegetative symptoms (eg, sleep and appetite disturbances, somatic complaints).
- Cognitive dysfunction (eg, concentration difficulty, apathy).
- Signs of social withdrawal, isolation, and increased dependency.
- Atypical presentations (TABLE 2).[16]

The somatic symptoms of depression in the elderly are frequently attributed incorrectly to other medical problems or to aging.[17]

Depression with coexisting medical illness

Depression is common in the medically ill,[18] but the diagnosis is not always straightforward. Fewer than half of depressed patients with coexisting medical illness are diagnosed, and of these, only 30% receive appropriate treatment.[19]

Often, families and caregivers believe that depressive symptoms are to be expected in patients with medical illness. Further, the symptoms of depression and of medical conditions often overlap. However, it is a mistake to assume that all depressive symptoms are due to the medical illness and therefore do not need treatment. As part of the medical evaluation, it is important to investigate symptoms suggestive of depression (eg, fatigue, weight loss, impaired sexual function) and to treat empirically with antidepressant medication, particularly if the likelihood of underlying systemic illness is low.

Medications sometimes cause or exacerbate symptoms of depression; these include antihypertensives, anabolic steroids, histamine type-2 receptor blockers, anticonvulsants, levodopa, certain antibiotics, anti-inflammatory drugs, antiarrhythmic drugs, metoclopramide, baclofen, and benzodiazepines.

Bereavement

It is normal to have some symptoms of depression after the death of a loved one, although there is some ethnic variability. However, when intense symptoms persist after 2 months, it is advisable to reevaluate. The physician should especially consider antidepressant treatment when the patient has feelings of excessive guilt or worthlessness or thoughts that he or she would be better off dead. Withdrawing from family and friends is of great concern. Functional impairment and depression persisting 2 months often predict continued major depression at 13 and 25 months.[20,21]

ACUTE-PHASE MANAGEMENT

Whenever possible, the practitioner and patient should decide together what type of treatment to use: medication, psychotherapy, medication and psychotherapy combined, electroconvulsive therapy, or, for seasonal affective disorder, light therapy. Such shared decision-making is likely to increase adherence and effectiveness. TABLE 3 outlines factors that affect the choice of treatment in the acute phase.[22]

If the depressive episodes are milder, less chronic, nonrecurrent, and nonpsychotic, the physician may wish to extend the evaluation over two or three visits and monitor the symp-

toms, to determine if the patient may improve with psychotherapy alone, without needing further intervention.

The most effective type of treatment is a combination of psychotherapy and medication. Psychiatrists are more likely than primary care physicians to provide this treatment.[23] Primary care providers often emphasize pharmacologic treatment and are reported to prescribe drugs for patients with psychiatric diagnoses 50% more often than psychiatrists.[24] This is perhaps more true for benzodiazepines used for anxiety disorders. On the other hand, primary care doctors tend to prescribe antidepressants at a lower dosage than may be therapeutic.

The most effective types of psychotherapy for major depression have been cognitive behavioral psychotherapy and interpersonal psychotherapy. Both of these are very specific manual-driven therapies and are not offered by all mental health professionals. Supportive counseling alone is certainly not considered adequate treatment for major depression but may be helpful in increasing the patient's adherence to the medication. It also gives the opportunity to discuss fears of taking "drugs" (antidepressants) and side effects that might require alteration of the prescription. This supportive counseling in conjunction with the medication can clearly be offered by the primary care physician.

If suicidal thoughts are mentioned, they require exploration. It is best to make a psychiatric referral whenever there is concern about the patient's safety.

Reasons to use a particular drug

No single antidepressant is clearly more effective than another; the reported rates of initial response are as high as 60% to 70% for all available agents vs about 20% for placebo.[25] Empirical trials are the only way to select the best drug for a particular patient, but several factors make the process more rational.

Age. The elderly tend to better tolerate antidepressants with fewer anticholinergic effects, such as selective serotonin reuptake inhibitors (SSRIs), bupropion, and secondary-amine tricyclics.

A previous response to a particular drug, in the patient or a first-degree family member, is an indication to try the same drug again.

TABLE 3

Indications for different treatments for depression

Medication alone
- Chronic depression
- Failure to respond to psychotherapy
- Family history of depression
- Melancholic cases
- More severe depression
- Patient preference
- Prior positive response
- Psychosis
- Recurrent episodes

Psychotherapy alone
- Availability
- Contraindication to medication
- Less chronic cases
- Less severe cases
- Nonpsychotic cases
- Patient preference
- Prior positive response

Combination therapy
- Availability
- Chronic cases
- More severe cases
- Partial response to either therapy alone
- Patient preference
- Personality disorder

Electroconvulsive therapy
- Contraindication to medication
- Failure of other therapies
- Need for rapid response
- Prior positive response
- Psychotic cases
- Very severe cases

All antidepressants produce response rates of 60% to 70%

Side-effect profile. An extensive review of side effects of antidepressant medications is beyond the purpose of this article, and has been done by Muzina and Malone[26] in the November/December 1996 issue of this journal. The most common side effects are outlined in TABLE 4.[22,27] Tricyclic antidepressants, although less expensive, tend to cause more side effects than SSRIs and the other newer antidepressants. Among the tricyclics the tertiary amines such as amitriptyline, doxepin, and imipramine tend to produce more side effects (especially anticholinergic) than the secondary amines such as desipramine and nortriptyline.

TABLE 4

Common side effects of antidepressant medications*

DRUG	ANTICHOLINERGIC EFFECTS	DROWSINESS	INSOMNIA	ORTHOSTATIC HYPOTENSION	ARRHYTHMIA	GI EFFECTS	WEIGHT GAIN
Tricyclics							
Tertiary amines (amitriptyline, doxepin, imipramine)	3–4	3–4	0–1	2–4	2–3	0–1	3–4
Secondary amines (desipramine, nortriptyline, protriptyline)	1–2	1	0–1	2	2	0	0–1
Other tricyclic antidepressants							
Amoxapine	2	2	2	2	3	0	1
Bupropion	0	0	2	0	1	1	0
Maprotiline	2	3	0	0	1	0	2
Mirtazapine	3	4	0	1	0–1	1	0
Trazodone	0	4	0	1	1	1	0
Venlafaxine	1	0–1	2	0–1	0	4	0
Selective serotonin reuptake inhibitors							
Fluoxetine	0	0–1	2–3	0	0	3	0
Fluvoxamine	1	0–1	2	0	0	4	0
Paroxetine	2	1–2	2	0	0	3	0
Sertraline	0	0–1	2	0	0	3	0
Monoamine oxidase inhibitors	1	1	2	2	0	1	2

*0 = none, 1 = mild, 2 = moderate, 3 = moderate to severe, 4 = severe

SOURCE: DATA FROM US DEPARTMENT OF HEALTH AND HUMAN SERVICES, REFERENCE 20, AND VEITH ET AL, REFERENCE 26

SSRIs can increase the levels of many drugs, including warfarin

Patients with heart disease should receive drugs such as SSRIs or bupropion, which are not associated with hypotension or cardiac conduction changes.[28,29] Patients with a history of seizures should not receive antidepressants that lower the threshold for seizures, such as clomipramine, maprotiline, amoxapine, and bupropion.[30]

Concurrent nonmood psychiatric disorders can sometimes be treated with a single agent for both conditions. Clomipramine and fluoxetine, for example, have been found effective in both depression and obsessive-compulsive disorder.

Interactions with drugs or food. All available antidepressants can have significant drug interactions.

SSRIs inhibit the hepatic cytochrome systems responsible for metabolizing many other drugs. Of the 34 known cytochrome isoenzymes, SSRIs can inhibit five (1A2, 2C9, 2C19, 2D6, and 3A4). This interaction can increase the levels of many commonly used drugs, including tricyclics, benzodiazepines, antipsychotics, some anticonvulsants (phenytoin and carbamazepine), antiarrhythmics, omeprazole, cisapride, warfarin, terfenadine, astemizole, beta-blockers, and calcium channel blockers.[26] Conversely, other drugs that also increase serotonin availability (eg, trazodone, tricyclics, monoamine oxidase inhibitors [MAOIs], L-tryptophan) can interact with SSRIs, leading to a rapid buildup of serotonin levels and a constellation of symptoms termed the "serotonin syndrome."[31]

Monoamine oxidase inhibitors should be avoided as first-line treatment in primary care, because of potentially lethal interactions with vasoconstrictors, decongestants, meperidine, and other antidepressants, as

well as the risk of inducing hypertensive crises with certain foods (eg, cheese, yogurt, sour cream, beer, broad beans, and active yeast preparations).

Need for serum level monitoring. Patients require monitoring of serum drug levels if they are highly vulnerable to toxicity, have uncertain compliance, or take multiple drugs with potential interactions. Such patients might be prescribed antidepressants with well-established therapeutic and toxic levels, such as nortriptyline, desipramine, and imipramine.

Risk of overdose. For patients at significant risk of overdose, special caution should be taken when prescribing tricyclic antidepressants. Tricyclics have been reported to be the third most common cause of drug-related death (following alcohol-drug combinations and heroin).[32] From 70% to 80% of patients who take overdoses of tricyclics do not reach the hospital alive.[33] The newer agents offer an important advantage in their wider margin of safety in overdose.

Cost. Tricyclic antidepressants are significantly less expensive than SSRIs per pill; however, the Boston Consulting Group found that SSRIs are cheaper in the long run because they entail less physician labor and fewer hospitalizations.[34] In addition, SSRIs tend to be better tolerated, easier to titrate, safer to use, more likely to be taken as directed, and less likely to lead to a relapse.[26]

Starting drug therapy

Before starting antidepressant drug therapy, it is important to determine if the patient has bipolar disorder, because virtually every available antidepressant agent can cause mania in patients with bipolar disorder.[35,36] Antidepressant drugs are not contraindicated in such patients, but they should be used cautiously: at the lowest effective dose, for the shortest time necessary,[37] and in conjunction with a mood stabilizer (eg, lithium, valproic acid, or carbamazepine).

TABLE 5 lists the class, starting dose, and target dose of antidepressant drugs.[38,39] Older adults generally need lower doses.

Tricyclic antidepressants. Before starting a tricyclic antidepressant, check the baseline heart rate, blood pressure (seated and

TABLE 5

Drugs used for depression

DRUG	STARTING DOSE (MG/DAY)	USUAL DOSE (MG/DAY)
Tricyclic antidepressants		
Tertiary amines		
Amitriptyline (Elavil)	25–50	100–300
Clomipramine (Anafranil)	25	100–250
Doxepin (Sinequan, Adapin)	25–50	100–300
Imipramine (Tofranil)	25–50	100–300
Trimipramine (Surmontil)	25–50	100–300
Secondary amines		
Desipramine (Norpramin)	25–50	100–300
Nortriptyline (Aventyl, Pamelor)	25	50–200
Protriptyline (Vivactil)	10	15–60
Other tricyclic antidepressants		
Amoxapine (Asendin)	50	100–400
Bupropion (Wellbutrin)	200	300–450
Maprotiline (Ludiomil)	50	100–225
Mirtazapine (Remeron)	15	15–45
Nefazodone (Serzone)	100	200–600
Trazodone (Desyrel)	50	150–500
Venlafaxine (Effexor)	37.5	75–375
Selective serotonin reuptake inhibitors		
Fluoxetine (Prozac)	5–20	20–80
Fluvoxamine (Luvox)	50	50–300
Paroxetine (Paxil)	10–20	20–50
Sertraline (Zoloft)	50–100	50–200
Monoamine oxidase inhibitors		
Phenelzine (Nardil)	15	15–90
Selegiline (Eldepryl)	5	10
Tranylcypromine (Parnate)	10	10–40
Adjuvants		
Carbamazepine (Tegretol)	200–400	400–1200
Lithium (Eskalith, Lithobid, others)	300	600–900
Levothyroxine (Synthroid)	25 µG	25–50 µG
Valproic acid (Depakene, Depakote)	250–500	500-1500
Verapamil (Calan, Dilacor)	80	120–240
Stimulants		
Methylphenidate (Ritalin)	2.5–5	10–40
Pemoline (Cylert)	18.75	18.75–75
Dextroamphetamine (Dexedrine)	2.5	10–40

TABLE 6

Instructions for patients taking antidepressants

Take the medication every day
Expect noticeable improvement from the medication in 2–4 weeks
Continue taking the medication even if you feel better
Do not stop taking the medication without notifying your physician
Contact your physician with any question

standing), and renal and hepatic function. In addition, an electrocardiogram should be ordered in patients older than 40 years or with significant risk of coronary artery disease. Tricyclics must be monitored carefully and used cautiously or not at all in patients with baseline conduction abnormalities (eg, a PR interval > 200 msec, corrected QT interval > 440 msec), significant orthostatic hypotension (ie, a fall in systolic blood pressure of > 15 mm Hg when standing), tachycardia (heart rate > 100), or a ventricular or atrial arrhythmia.[28,40,41]

Symptoms may take up to 12 weeks to resolve

In patients with low-grade conduction disease (first-degree block, uncomplicated right or left bundle-branch block, or hemiblock), the tricyclic antidepressants must be used with caution because a higher degree of heart block could develop. In patients with more advanced conduction disease (bifascicular or trifascicular block, second- or third-degree block), tricyclic antidepressants are relatively contraindicated without a pacemaker.[29]

When using tricyclics, the initial dose should be gradually raised as tolerated, starting with a low daily dose given at bedtime, until a therapeutic dose is reached. The rate of increase will vary from person to person, but can be done at 3- to 4-day intervals.

Follow-up is vital

Regardless of what treatment the patient and physician select, frequent follow-up is vital during the initial stages of therapy. Visits should be scheduled weekly or biweekly to monitor the patient's tolerance to medication and clinical course until symptom relief becomes evident. If this type of follow-up is not possible, regular telephone contact should be arranged.

For all available antidepressant agents, the reported rates of initial response are as high as 60% to 70% vs approximately 20% for placebo.[25] Patients may show some improvement by the end of the first week,[42] but may not fully respond before 4 to 6 weeks, or up to 12 weeks in geriatric patients.[43,44] Therefore, adequacy of response cannot be judged until this time.

Nonadherence is a major obstacle to effective treatment. A recent study at a large health maintenance organization[45] found that 30% to 40% of patients who are started on antidepressants drop out of treatment within the first 30 days. Katon et al[18] found that up to 60% of primary care patients stopped taking their prescribed antidepressants before completing the recommended 6 months of therapy. These investigators showed that a brief discussion about the nature and course of depression (TABLE 6) is likely to improve compliance.

CONTINUE TREATMENT TO AVOID RELAPSE

After an antidepressant produces a satisfactory response, it should be continued in a full therapeutic dose for at least 6 months after remission from a first episode and 12 months for a second episode.[46,47]

MAINTENANCE TREATMENT

Depression is a recurrent disorder. Patients may be prone to recurrences and should be considered for continuous prophylactic treatment if they have any of the following:

- Persistent dysthymic symptoms after recovery from a depressive episode.
- An additional nonaffective psychiatric diagnosis.
- A chronic medical condition.
- Multiple episodes of depression[48] (three or more episodes, or two or more severe episodes, or two episodes plus a family history of unipolar or bipolar disorder).[22,49]
- A first episode before age 20.
- A recurrent episode within 1 year after effective therapy is discontinued.[22,49]

The options for maintenance treatment include the various antidepressants and lithi-

um.[50,51] Antidepressants should be continued at full therapeutic doses. The timing and method of discontinuing maintenance therapy have not been systematically studied, but tapering, rather than abrupt discontinuation, is generally recommended because of the risk of cholinergic rebound with some medications.[52] Another reason for tapering rather than abrupt discontinuation is that if symptoms are going to reemerge, they will be less severe and more easily treated.

Maintenance psychotherapy should be considered for patients with unresolved intrapsychic or interpersonal conflicts that are distressing and that are thought to predispose the patient to recurrent episodes.[38]

MANAGING RESISTANT DEPRESSION

Initial treatment fails to achieve a response in approximately 20% to 30% of patients. In some cases the apparent lack of response is actually a result of faulty diagnosis, inadequate treatment, or failure to appreciate and remedy coexisting general medical or psychiatric conditions.[53] Adequate treatment for at least 6 to 12 weeks is required before concluding that the patient is not responsive.[22] In resistant depression, the following strategies are recommended:

- Review the diagnosis for appropriateness and coexisting medical and psychiatric conditions.
- Add an adjunctive agent to an antidepressant (TABLE 5).
- Use multiple antidepressants simultaneously.
- Consider electroconvulsive therapy.
- Consider anticonvulsants: carbamazepine and valproic acid have demonstrated some benefit.[54,55]

SECOND OPINIONS AND REFERRALS

Depression is eminently treatable in primary care. Physicians should aim for optimal regulation and complete remission, not partial improvement, since incomplete treatment makes subsequent treatment more difficult. Therefore, practitioners should not delay seeking a consultation when needed (TABLE 7).[22]

TABLE 7

Indications for referral

- Diagnostic consultation
- Need for hospitalization
- Need for intense psychotherapy
- Need for light therapy
- Need for electroconvulsive therapy
- Partial response or medication-resistant depression
- Patient request
- Poor adherence
- Severe, recurrent, or psychotic depression
- Substance abuse or dependence
- Suicidal patients
- Symptom breakthrough after a positive acute-phase response

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Obtain an ECG when starting a tricyclic in a patient older than 40

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