Review Article

Primary Care

MANAGING DEPRESSION IN MEDICAL OUTPATIENTS

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DEPRESSION is second only to hypertension as the most common chronic condition encountered in general medical practice.[1] At least 1 in 10 outpatients has major depression, but most cases are unrecognized or inappropriately treated,[2-4] leading to loss of productivity, functional decline, and increased mortality.[5-9] Appropriate therapy improves the daily functioning and overall health of patients with depression.[10,11]

DIAGNOSIS

Major depression is defined by depressed mood or loss of interest in nearly all activities (or both) for at least two weeks, accompanied by a minimum of three or four of the following symptoms (for a total of at least five symptoms altogether): 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 (Fig. 1).[12] Among patients with major depression, the level of illness ranges from mild to severe (Table 1).

It is unclear whether all patients in primary care settings should be screened routinely for depression. Screening alone does not improve outcomes for patients with unrecognized depression,[13-16] but screening in combination with patient-support programs, such as frequent nursing follow-up and close monitoring of adherence to therapy, may be useful.[17] Even if patient-support programs are unavailable, we recommend routine case finding (screening of selected patients) among those whose profile suggests increased risk, such as those with a family or personal history of depression, multiple medical problems, unexplained physical symptoms, chronic pain, or use of medical services that is more frequent than expected.[18-21] Many validated case-finding instruments can be used to detect depression among patients in primary care,[22] including two simple questions about depressed mood and anhedonia (Fig. 1).[23] Since this method has a sensitivity of 96 percent but a specificity of only 57 percent, additional questions are needed to confirm the diagnosis of depression (Fig. 1).

Some symptoms of depression can be confused with those of other medical illnesses. For example, weight loss and fatigue may also be associated with disorders such as diabetes, cancer, and thyroid disease. The history and physical examination should guide any further diagnostic workup. Since depression is a clinical diagnosis, no routine laboratory tests are necessary, although measurement of serum thyroid-stimulating hormone is indicated for women more than 65 years of age and for patients with additional signs or symptoms of hypothyroidism.[24] The use of benzodiazepines and narcotics is associated with depression, but few nonpsychotropic medications, except for glucocorticoids and reserpine, cause depressive symptoms.[25] Beta-blockers do not cause depression.[26]

ASSESSMENT OF THE RISK OF SUICIDE

Depressed patients frequently contemplate suicide. Depressed men are more likely to commit suicide than depressed women, with the highest rate among elderly white men (Table 2).[27-29] The initial evaluation must include specific questions, such as, "Do you ever think of hurting yourself or taking your own life?" If the answer is yes, this should be followed by "Do you currently have a plan?" and, if the answer is yes, "What is your plan?"[30] Practitioners should not avoid these questions for fear of suggesting the idea of suicide. If patients are unsure of their ability to resist suicidal urges, or if providers are concerned that certain patients may not seek help before harming themselves, emergency psychiatric evaluation becomes critical. Even in the absence of immediate risk, providers should emphasize to patients the importance of reporting suicidal thoughts, especially if they are becoming more intense or more frequent.

NEED FOR TREATMENT

We view major depression as a continuum of illness that varies in severity and duration, rather than as a rigid, criteria-based diagnosis.[31,32] Whether to initiate specific treatment depends on the probability that the

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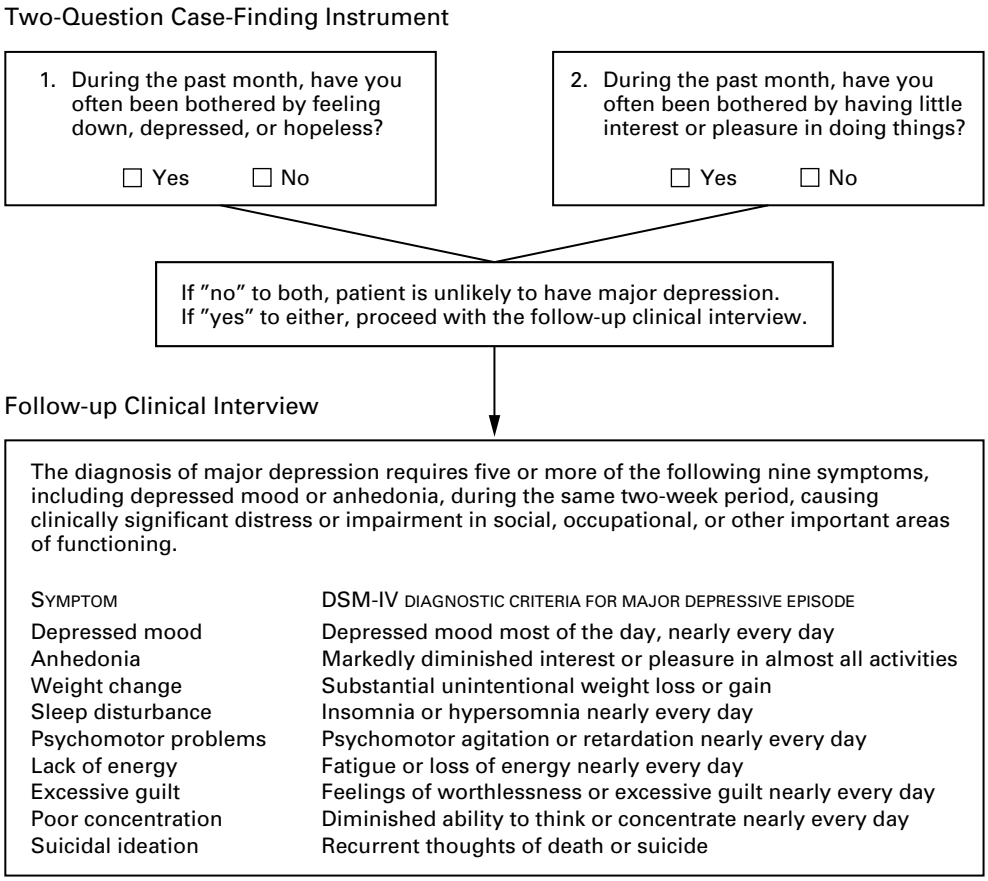

Figure 1. Diagnostic Algorithm for Major Depression.
Adapted from the *Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition*[12] (DSM-IV).

patient will recover spontaneously during the next two to four weeks. Patients who have moderate-to-severe symptoms, substantial functional impairment, or a long duration of illness are unlikely to recover quickly and deserve immediate treatment. For patients with less severe or less persistent symptoms, a trial of support and encouragement, with reevaluation in two to four weeks, may be considered, but treatment should be initiated if symptoms persist after a few weeks of watchful waiting.

Antidepressant medication and structured psychotherapy are effective treatments for major depression.[33] Patients with dysthymia (characterized by fewer than five depressive symptoms that persist for two or more years) may also benefit from antidepressant therapy.[34,35] It is unclear, however, whether patients with minor depression (characterized by fewer than five depressive symptoms that persist for less than two years) have higher recovery rates with specific treatment or with supportive care and watchful waiting.[15,35,36] Since normal bereavement can lead to major depression, grieving patients who have symptoms of depression lasting longer than two months should be offered antidepressant therapy.

Providers must treat depression aggressively in patients with other medical problems, because depression increases patients' sensitivity to somatic distress, leads to poorer self-care, and worsens the prognosis associated with disorders such as cardiovascular disease.[37,38] Appropriate therapy reduces depressive symptoms and improves overall well-being.[39] Since mild cognitive impairment, with poor concentration and psychomotor retardation, may result from either depression or dementia, a trial of antidepressant therapy should be initiated in patients with apparent dementia who meet diagnostic criteria for major depression.[40]

Other psychiatric disorders frequently coexist with depression. In patients with concurrent anxiety, the provider should treat the depression first, since doing so may improve the symptoms of both disorders.[41,42] Patients with a history of mania (elevated mood, increased energy, and impulsivity), psychosis (hearing voices or seeing things that are not there), or another major psychiatric illness should be referred for psy-

TABLE 1. DIAGNOSTIC CATEGORIES FOR DEPRESSION.

DIAGNOSTIC CATEGORY	CRITERIA*	DURATION
Minor depression	2 to 4 depressive symptoms, including depressed mood or anhedonia†	≥2 wk
Dysthymia	3 or 4 dysthymic symptoms, including depressed mood‡	≥2 yr
Major depression	≥5 depressive symptoms, including depressed mood or anhedonia	≥2 wk
Mild	Few (if any) symptoms in excess of those required for the diagnosis; minimal impairment in functioning	
Moderate	Greater number and intensity of depressive symptoms; moderate impairment in functioning	
Severe	Marked intensity and pervasiveness of depressive symptoms; substantial impairment in functioning	

*Criteria are from the *Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition*,[12] which includes diagnostic criteria for major depression and dysthymia but only research criteria for minor depression.

†Depressive symptoms include depressed mood, anhedonia, weight change, sleep disturbance, psychomotor problems, lack of energy, excessive guilt, poor concentration, and suicidal ideation.

‡Dysthymic symptoms include depressed mood, poor appetite or overeating, sleep disturbance, lack of energy, low self-esteem, poor concentration, and hopelessness.

TABLE 2. RISK FACTORS FOR SUICIDE IN PATIENTS WITH MAJOR DEPRESSION.

Age greater than 65 years
Male sex
White race or Native American ethnic background
Single, divorced, separated, or widowed status (especially without children)
Unemployment
History of admission to a psychiatric ward
Family or personal history of one or more suicide attempts
Drug or alcohol abuse
Severely stressful life event in recent past
Panic attacks or severe anxiety
Severe physical illness (especially of recent onset)
Severe hopelessness or anhedonia
Specific plan for suicide (especially with high potential lethality)
Access to firearms or other lethal means

chiatric evaluation. Substance abuse, which is common among depressed patients, must not be considered a contraindication to therapy. Aggressive treatment of depression can decrease the use of tobacco,[43] alcohol,[44] and possibly other drugs of abuse.

EDUCATION OF PATIENTS

Despite public-education efforts, depression frequently carries a stigma and may be viewed as a moral weakness or character flaw. Appropriate education can help patients understand their condition as resulting from a combination of an inherited predisposition and accumulated biologic and psychosocial stress. Some patients focus on physical problems and interpret a diagnosis of depression as a doctor's decision that "It's all in your head." Providers can explain that physical problems and sleep disturbances are characteristic of depression and that effective relief of depression often makes chronic illness and physical symptoms more bearable. Emphasizing the high prevalence of depression may also help decrease the stigma associated with this illness. Several Internet resources may be of help (Table 3).

OPTIONS FOR TREATMENT

Fifty to 60 percent of depressed patients in primary care settings respond to initial treatment with pharmacotherapy or structured psychotherapy.[31] The choice of treatment depends on availability and the patient's preference. Although there is some evidence that pharmacotherapy may be more effective than psychotherapy for severe depression, this has not been clearly established for patients in primary care.[31] Combined therapy may be preferable for patients with recurrent depression and for those whose condition has not responded to either treatment alone.[45,46]

Supportive Care

Few primary care physicians have the training or time to provide formal psychotherapy, but brief counseling can incorporate several of its effective elements, including encouraging patients to schedule relaxing or enjoyable activities every day, identifying exaggerated negative or self-critical thoughts, encouraging patients to develop more realistic self-perceptions, and breaking current life problems into smaller components as well as identifying specific steps to address them.[47] Primary care providers can offer brief supportive counseling as initial treatment for patients with mild depression or as an adjunct to pharmacotherapy. Self-help books may further support patients' use of these cognitive and behavioral techniques.[48]

Pharmacotherapy

Selection of Medication

How antidepressant medications achieve their therapeutic benefit is not completely understood. No single drug has proved more effective than any other for the relief of depressive symptoms,[49] but specific drugs may be more useful for associated conditions such as panic disorder, pain syndromes, or obsessive–compulsive disorder (Table 4).

More than 80 percent of depressed patients have a response to at least one medication, although individ-

TABLE 3. SELECTED INTERNET RESOURCES ON DEPRESSION.

ORGANIZATION	INTERNET ADDRESS
Agency for Healthcare Research and Quality	http://text.nlm.nih.gov (select "AHCPR Supported Guidelines" and then "Depression in Primary Care")
American Medical Association	http://www.ama-assn.org/consumer/specond.htm
Depression Awareness, Recognition, and Treatment program of the National Institute of Mental Health	http://www.nimh.nih.gov/publicat/index.cfm
National Depressive and Manic–Depressive Association	http://www.ndmda.org
National Foundation for Depressive Illness	http://www.depression.org
National Mental Health Association	http://www.nmha.org/ccd
Psychology Information Online	http://www.psychologyinfo.com/depression

ual antidepressants are effective in only 50 to 60 percent of patients.[33] Factors that may be considered in selecting a particular antidepressant include a previous response to that medication, a family history of a response to the same medication, and anticipated side effects (Table 5).[41] Anxiety and insomnia do not necessarily predict a better response to more sedating medications.[52-54] Although selective serotonin-reuptake inhibitors cost more than tricyclic antidepressants, the total costs of treatment with these two drug classes are usually similar because of the increased number of visits associated with switching to the more expensive medications in some patients who begin with tricyclic agents.[55] Newer antidepressants are generally less toxic than tricyclics in cases of overdose but do not reduce the overall risk of suicide.[56]

Dosage

Table 4 lists the initial doses for commonly prescribed antidepressants. Patients should be instructed to increase the dose gradually, approaching the target dose over a period of 5 to 10 days. Starting doses should be lower for patients with hepatic or renal insufficiency and for elderly patients, although the effective doses for elderly patients may be similar to those for younger adults. Given the potential for overdose in depressed patients, no more than a month's supply of antidepressant medication should be dispensed initially.

If no improvement occurs within three to four weeks and the side effects are tolerable, the dose should be increased to the step-up dose (the dose above which most patients would not derive additional benefit). If intolerable side effects occur and persist or if there is little or no improvement after three to four weeks at the step-up dose, a trial of an alternative medication should be considered.[33] Regardless of the dose, full therapeutic effects may not be evident for four to six weeks. Although measurement of serum drug levels is not routinely recommended, it may prove helpful in patients who have severe side effects at a low dose or no response at a relatively high dose (such tests are generally available for tricyclic antidepressants and trazodone). Measurement of serum levels is not useful for selective serotonin-reuptake inhibitors. Once-daily medications may be taken in the morning or evening, depending on their activating or sedating side effects, which vary among patients.

Side Effects

Side effects differ among drug classes (Table 5), and effects within drug classes vary among patients. Most side effects diminish over a period of one to four weeks, but since benefits are slow to occur, encouragement during the early phase of treatment is essential. Weight gain and sexual dysfunction may persist longer than other side effects. If the patient has insomnia, 50 to 100 mg of trazodone can be added at bedtime.

Cautions and Interactions

Since the cardiovascular effects of tricyclic antidepressants include postural hypotension (particularly in the elderly), cardiac conduction abnormalities, and arrhythmias, the use of these drugs should be avoided in patients with ischemic heart disease or known arrhythmias, whenever possible.[57] Before therapy with a tricyclic agent is initiated in any patient over the age of 50 years, it is prudent to obtain an electrocardiogram. If first-degree atrioventricular block or bundle-branch block is present, the electrocardiogram should be repeated after any increase in the dose.

Nearly all antidepressant medications are eliminated primarily through hepatic metabolism, so they should be used with caution in patients with liver disease. Selective serotonin-reuptake inhibitors (especially fluoxetine) may cause drug interactions because of their inhibition of the cytochrome P-450 system.[50] Patients taking selective serotonin-reuptake inhibitors should

TABLE 4. SELECTED ANTIDEPRESSANTS FOR USE IN MEDICAL OUTPATIENTS.*

CATEGORY AND GENERIC NAME	TRADE NAME	INITIAL DOSE†	TARGET DOSE‡	STEP-UP DOSE‡	OTHER INDICATIONS	COST PER MONTH§
Serotonin- and norepinephrine-reuptake inhibitors						
Tricyclics (tertiary amines)						
Amitriptyline	Elavil, Endep	25 mg at bedtime	100 mg at bedtime	150 mg at bedtime	Chronic pain, delusions,¶ insomnia, migraine, postherpetic neuralgia	$8.43
Doxepin	Sinequan	25 mg at bedtime	100 mg at bedtime	150–200 mg at bedtime	Alcoholism,¶ insomnia, post-traumatic stress disorder	$11.85
Imipramine	Tofranil	25 mg at bedtime	100 mg at bedtime	150–200 mg at bedtime	Enuresis,¶ insomnia, panic disorder, post-traumatic stress disorder, obsessive–compulsive disorder	$42.24
Tricyclics (secondary amines)						
Desipramine	Norpramin	25 mg at bedtime	100 mg at bedtime	150–200 mg at bedtime	Attention-deficit disorder,¶ bulimia, diabetic neuropathy, postherpetic neuralgia	$32.98
Nortriptyline	Aventyl, Pamelor	25 mg at bedtime	50–75 mg at bedtime	100–150 mg at bedtime	Attention-deficit disorder, chronic low back pain, irritable bowel syndrome, diabetic neuropathy	$45.88–$70.65
Bicyclic						
Venlafaxine	Effexor	37.5 mg twice daily	75 mg twice daily	100–150 mg twice daily	Anxiety disorder,¶ neuropathic pain, obsessive–compulsive disorder	$78.71
	Effexor XR	37.5 mg daily	75–150 mg daily	225 mg daily		$69.65–$75.86
Selective serotonin-reuptake inhibitors						
Citalopram	Celexa	20 mg daily	20 mg daily	40 mg daily	Obsessive–compulsive disorder, diabetic neuropathy, post-stroke depression,¶ panic disorder	$60.51
Fluoxetine	Prozac	20 mg every morning	20 mg every morning	40–60 mg every morning	Bulimia,¶ obsessive–compulsive disorder¶	$67.36
Paroxetine	Paxil	20 mg daily	20 mg daily	50 mg daily	Obsessive–compulsive disorder,¶ panic disorder,¶ migraine, social phobia¶	$69.86
Sertraline	Zoloft	50 mg every morning	100 mg every morning	150–200 mg every morning	Obsessive–compulsive disorder, panic disorder,¶ post-traumatic stress disorder	$72.29
Serotonin antagonist						
Mirtazapine	Remeron	15 mg at bedtime	30 mg at bedtime	45 mg at bedtime	Anxiety, insomnia	$71.83
Norepinephrine- and dopamine-reuptake inhibitor						
Bupropion	Wellbutrin	75 mg twice daily	150 mg twice daily	150 mg three times daily	Attention-deficit disorder, smoking cessation,¶ post-traumatic stress disorder	$96.11
	Wellbutrin SR	150 mg every morning	150 mg twice daily	200 mg twice daily		$91.64
Serotonin antagonists and reuptake inhibitors						
Nefazodone	Serzone	100 mg twice daily	150 mg twice daily	300 mg twice daily	Panic disorder, post-traumatic stress disorder	$74.11
Trazodone‖	Desyrel	50 mg at bedtime	200 mg at bedtime	200 mg twice daily	Insomnia	$21.98

*The information provided in this table is intended only as a guide. Providers should refer to the package inserts or consult with a pharmacist for individual dosage recommendations, precautions, and drug interactions.

†The initial dose should be reduced in frail or elderly patients and in patients with hepatic or renal dysfunction.

‡The target dose is the dose likely to be effective for a typical patient. The step-up dose is the dose above which most patients would not derive additional benefit.[50]

§The average wholesale price in U.S. dollars for a 30-day supply of the target dose is given. Generic prices are used, when available. Data are from *2000 Drug Topics Red Book*.[51]

¶The drug is approved by the Food and Drug Administration for this indication.

‖Trazodone is too sedating at therapeutic doses for depression; it is best used in lower doses (50–100 mg at bedtime) as adjunctive therapy for patients with insomnia.

TABLE 5. FREQUENCY OF SIDE EFFECTS OF ANTIDEPRESSANT MEDICATIONS.*

MEDICATION	SEDATION	AGITATION	ANTICHOLINERGIC EFFECTS†	POSTURAL HYPOTENSION	GASTROINTESTINAL UPSET	SEXUAL DYSFUNCTION	WEIGHT GAIN	WEIGHT LOSS
Serotonin- and norepinephrine-reuptake inhibitors								
Tricyclics (tertiary amines)								
Amitriptyline	++++	0	++++	+++	+	+	++	0
Doxepin	++++	0	++++	+++	+	+	+	0
Imipramine	++++	0	++++	+++	+	+	+	0
Tricyclics (secondary amines)								
Desipramine	+++	0	+++	++	+	+	+	0
Nortriptyline	+++	0	+++	++	+	+	+	0
Bicyclic								
Venlafaxine‡	++	+	++	0	+++	++	0	+
Selective serotonin-reuptake inhibitors								
Citalopram	0	0	+	0	++	+	+	+
Fluoxetine	+	++	+	0	++	++	+	+
Paroxetine	++	0	+	0	++	++	+	+
Sertraline	+	+	+	0	++	++	+	+
Serotonin antagonist								
Mirtazapine	+++	0	++	+	0	0	++	0
Norepinephrine- and dopamine-reuptake inhibitor								
Bupropion	+	++	++	0	++	0	+	++
Serotonin antagonists and reuptake inhibitors								
Nefazodone	++	0	++	+	+	0	0	0
Trazodone	++++	0	++	+	+	0	+	+

*0 denotes none; +, minimal (<5 percent of patients); ++, low frequency (5–20 percent); +++, moderate frequency (21–40 percent); ++++, high frequency (>40 percent).

†Side effects may include dry mouth, dry eyes, blurred vision, constipation, urinary retention, tachycardia, or confusion.

‡Venlafaxine may cause a dose-related elevation in diastolic blood pressure; monitoring of blood pressure is recommended.

not take sibutramine. Single doses of more than 200 mg of bupropion or total daily doses of more than 450 mg may increase the risk of seizures. Trazodone causes priapism in rare cases.

Herbal Remedies

Hypericum perforatum (St. John's wort), an herbal remedy marketed as a dietary supplement, appears to be more effective than placebo and as effective as low-dose tricyclic antidepressants for the treatment of mild depression.[58,59] Side effects are infrequent. Other herbal remedies, such as kavakava or valerian root, have not proved effective for the treatment of depression.[49]

Structured Psychotherapy

Cognitive–behavioral therapy, problem-solving therapy, and interpersonal psychotherapy are effective treatments for major depression. Cognitive therapy focuses on identifying and challenging pessimistic or self-critical thoughts that cause or perpetuate depression. Behavioral therapy, which is often combined with cognitive therapy, emphasizes increasing involvement in rewarding activities and decreasing behavior that reinforces depression. Problem-solving therapy teaches patients to address current life difficulties by breaking larger problems into smaller pieces and identifying specific steps toward positive change. Interpersonal therapy aims at clarification and resolution of interpersonal difficulties, such as role disputes, social isolation, prolonged grief, or role transition. These structured psychotherapies should be provided by a qualified psychotherapist, typically for 6 to 16 sessions. Psychoanalytic or psychodynamic therapies have not proved effective for patients in primary care.[33]

Referral to a Psychiatrist

Although primary care clinicians can provide effective therapy for more than 75 percent of patients with depression,[41] we recommend psychiatric consultation for patients with a history of mania or psychosis, for those whose condition has not responded to trials of one or two medications, and for those who require combination therapy. Immediate psychiatric evaluation is necessary whenever there is a danger that patients will harm themselves.

FOLLOW-UP

Pharmacotherapy

Close follow-up during the first three months of treatment is crucial. Nearly half of medical outpatients who receive an initial prescription for an antidepressant discontinue treatment during the first month, and few receive the recommended levels of follow-up care.[2,3] Patients should have a minimum of three visits during the first 12 weeks of antidepressant treatment,[60] and some guidelines recommend follow-up contact every 1 to 2 weeks until substantial improvement has occurred.[41]

Organized follow-up programs improve the quality of care and outcomes for depressed patients in primary care and are cost effective.[11,17,36,61-64] Elements common to these programs include education of the patient and the physician, monitoring of adherence to medication, active follow-up, and psychiatric consultation as needed.[65] Telephone contact may be substituted for some in-person visits.[66,67] If the patient agrees, it also may be helpful to enlist family members to monitor symptoms and encourage compliance with therapy.

Patients must be aware that antidepressants take at least four to six weeks to have a full therapeutic effect and that only about half of patients respond to the first medication prescribed. Patients who have not responded to a medication or who have had intolerable side effects may be switched either to a different class of antidepressants or to another medication within the same class. Failure to respond to one selective serotonin-reuptake inhibitor, for example, does not necessarily predict nonresponse to other selective serotonin-reuptake inhibitors. No washout period is necessary when switching among selective serotonin-reuptake inhibitors or between a selective serotonin-reuptake inhibitor and a tricyclic antidepressant. However, abruptly discontinuing shorter-acting serotonergic drugs (such as citalopram, paroxetine, sertraline, or venlafaxine) may result in a discontinuation syndrome with tinnitus, vertigo, or paresthesias. If a trial of a second medication is not beneficial, or if symptoms worsen, psychiatric consultation is recommended.

Once symptoms are relieved, pharmacotherapy should be continued for at least six months to prevent relapse.[68] Patients at high risk of relapse (those with two or more previous episodes or with major depression lasting more than two years) must continue pharmacotherapy for at least two years, and possibly indefinitely.[69] Follow-up visits should be scheduled every three to six months. A return of symptoms indicates the need for adjustment of the dosage, a change of medication, or psychiatric consultation. If the patient and physician agree on a trial discontinuation of the medication, withdrawal should be gradual, with tapering over a period of two to three months, and at least monthly follow-up, in person or by telephone. If depression recurs, the patient should promptly resume taking medication for at least three to six months.

Structured Psychotherapy

A referral for psychotherapy does not relieve the referring physician of follow-up obligations, since premature discontinuation of psychotherapy is even more common than premature discontinuation of pharmacotherapy.[70] The clinical benefits of psychotherapy should be evident within six to eight weeks. Medication must be considered for patients whose symptoms fail to improve by that time, and for those who do not have a full remission after 12 weeks of psychotherapy. The available data are insufficient to justify recommending extended psychotherapy for the prevention of a recurrence.[71]

PROGNOSIS

Depression is often chronic, with alternating relapses and remissions.[72] About one third of patients with a single episode of major depression will have another episode within one year after discontinuing treatment,[73] and more than half will have a recurrence during their lifetimes. Greater severity of depression, persistence of symptoms, and a higher number of prior episodes are the best predictors of recurrence.[74,75] Chronic depression frequently develops in patients with multiple recurrences.[76]

CONCLUSIONS

High-quality care for medical outpatients with depression is both achievable and affordable.[17] Primary care physicians can provide the essential elements of effective care for depression, including education of patients, prescription of medications, systematic follow-up, and appropriate use of specialists and resources. This comprehensive approach will improve patients' physical and psychological well-being.

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