

Current Perspectives on the Diagnosis and Treatment of Major Depressive Disorder

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Summary

Each year in America approximately 6 million people suffer from depression at a cost of more than \$16 billion. People who are depressed have more medical illnesses than those without depression and make greater use of healthcare services. In a 15-month period after having been diagnosed with depression, sufferers are 4 times more likely to die as those who do not have depression. Almost 60% of suicides have their roots in major depression, and 15% of those admitted to a psychiatric hospital for depression eventually kill themselves. Although depression is highly treatable, only one third of sufferers receive suitable treatment. The reason for underdiagnosis is 2-fold: Physicians may fail to recognize depression and sufferers may actively deny it. A family history of depression is an important cause in those who suffer recurrent episodes. Major depressive disorder is the most common type of depression and, unless treated, resolves by itself in 6 months to a year less than 40% of the time. Depressive symptoms can be found in as many as 30% of those who abuse alcohol, so abstinence is crucial to treatment. Contrary to popular belief, depression is not a normal part of aging, although it can occur in elderly people who have severe medical and psychosocial problems. The goal of pharmacotherapy is the reduction and ultimate removal of all signs and symptoms of depression. More than 2 dozen drugs with 7 distinct mechanisms of action are available to treat depression, with the clinical goal being remission. Whereas psychotherapy is a treatment option, by itself it tends to be effective in only a limited group of highly motivated individuals who have less severe forms of depression. As a result, treatment outcomes are better when pharmacologic antidepressant treatment and psychotherapy are combined.

Depression affects as many as 10% of men and 20% of women at some point in their lives; the estimated overall lifetime prevalence of depression in the United States is approximately 17%.¹ Significant depressive symptoms are seen in up to 36% of all medically ill patients.² Those with stroke, dementia, diabetes, heart disease, and renal impairment have especially high rates of comorbid depression.³⁻⁶ At any given time, about 6 million Americans suffer from depression, costing more than \$16 billion annually.⁷ Furthermore, the condition is one of the most frequent reasons for primary care visits.¹

Depressed people have more medical illnesses than nondepressed people,^{2,8} and they use healthcare services at higher rates.^{9,10} The prognoses of many diseases are worsened among depressed patients.^{9,10} In addition, depression may lead to significant psychosocial morbidity with diminished functioning in occupational or social roles.² In the 15 months after the diagnosis of depression, mortality rates among affected patients are 4 times higher than in age-matched control subjects.² Suicide contributes to the increased mortality. Nearly 60% of all suicides are related to major depression, and 15% of depressed patients admitted to a psychiatric hospital eventually commit suicide.²

Although depression is a common, highly treatable mood disorder, only one third of depressed people receive appropriate intervention.¹ The reasons for underdiagnosis vary from poor recogni-

tion and lack of screening by physicians to active denial by patients. The stigma associated with psychiatric conditions is probably the single most important factor to explain why the condition is underdiagnosed. Furthermore, depression is associated with direct and indirect costs that place an enormous burden on the health-care system.²

Diagnostic Considerations

People with a depressive disorder often seek help from their primary care physician (PCP) for various symptoms that rarely include “depression.” The disorder often presents in masked form with chronic fatigue, pain, or nonspecific somatic complaints. Depressed mood may be overt or may manifest as indifference, aloofness, uneasiness, “nerves,” agitation, or even anger. Therefore, a

high index of suspicion is needed, because many presenting symptoms may be those of depression rather than a somatic ailment.

Depression is characterized by dysphoria, dysfunction of sleep and appetite, absence of joy and pleasure, and in severe cases, suicidal ideation. Clinicians recognize several types of depression (Table 1).¹¹

Major depressive disorder (MDD) is the most common type of depression. The diagnostic criteria for MDD are listed in Table 2. Five of the 9 criteria must be met to establish the diagnosis.¹¹ The condition must be continuously present most, but not all, of the time for at least 2 weeks. This criterion is important, because some patients report brief periods of well-being as evidence they are not depressed. Either depressed mood or loss of pleasure and interest must be present by self-report or observation.

Dysfunction in social or occupational settings or a high level of subjective distress distinguishes depression from transient sadness, which is a normal part of the human experience. In people experiencing excessive sadness, levels of functioning and distress are proportional to life events. Clues to depression include a previous depressive illness or suicide attempt, a family history of mood disorder, lack of social support, stressful life events, abuse of alcohol and/or other substances, and concurrent chronic medical disease, pain, and/or disability.¹¹

A family history of depression is an important factor, particularly in patients with recurrent depression, melancholia (Table 3), insomnia, psychomotor changes, guilt, or early-onset depression (ie, before the age of 20 years).¹¹ These variants are likely to have heritable components; however, recent life events are probably the most important precipitant of relapse. In a study of nonmelancholic patients with recurrent depression,¹² 73% of episodes were related to a distressing life event. A prodromal phase of anxiety and mild depression precedes most major depressive episodes.¹¹

Table 1. Characteristics of Various Types of Depression

Diagnosis	Characteristics
Major depressive disorder	One or more major depressive episodes
Dysthymic and cyclothymic disorders	At least 2 years of predominantly depressed mood with other depressive symptoms, but not meeting criteria for major depression
Bipolar I disorder	At least 1 manic episode, usually accompanied by major depressive episodes
Bipolar II disorder	One or more major depressive episodes and at least 1 hypomanic episode
Depression as a result of general medical condition	Believed to be directly related to physiologic alteration brought about by an identified medical condition
Depression as a result of substance abuse	Believed to be directly related to physiologic alteration brought about by a toxin, medication, or drug of abuse
Depression not otherwise specified	Significant depression that does not meet criteria for major depressive disorder

Source: Reference 11.

Depressive symptoms are seen in up to 30% of people who abuse alcohol.¹³ Alcohol abuse is also probably more common among depressed people than the general population. In depressed patients who abuse alcohol, sobriety is an essential part of treatment.

Depression is not a normal part of aging. However, the condition occurs among older people who have severe medical and psychosocial problems and a concurrent reduction in coping capacity and resources. Recognition of depression in the elderly is complicated by coexisting medical or neurologic conditions that are common in this population (eg, stroke, dementia).

Many patients and physicians share the misbelief that depression in people who have a severe or disabling physical illness is appropriate and does not require treatment. Such patients can benefit greatly from treatment, because depression increases overall morbidity and mortality rates.²

Course and Prognosis

Untreated MDD resolves spontaneously less than 40% of the time within 6 months to 1 year.¹¹ In about 20% of cases, resolution is incomplete, and subclinical symptoms may persist for years. In the remaining 40% of people with MDD, symptoms continue longer than 1 year.¹¹

Depression is usually recurrent; half of those who have 1 depressive episode are likely to have at least 1 other occurrence in his or her lifetime.² The risk of recurrence increases to 70% after 2 depressive episodes and to 90% after 3 episodes.² Patients with recurrent depression are also more likely to have increased morbidity rates and a poorer long-term prognosis. Treatment can profoundly improve the short-term course; long-term treatment also prevents relapses and recurrences.¹⁴

Suicidal ideation and suicide attempts are common among depressed people. One in 8 suicide attempts is fatal, and about 3% of people who have previously attempted suicide eventually kill themselves.¹¹

Table 2. Diagnostic Criteria for Major Depressive Disorder

<p>Five of the following symptoms must be present during the same 2-week period; must include at least 1 of the first 2 symptoms (as indicated by self-report or observation).*</p> <ol style="list-style-type: none"> 1. Depressed mood most of the time 2. Markedly diminished interest or pleasure in nearly all activities most of the time 3. Unintentional 5% change in weight over 1 month, or a significant increase or decrease in appetite most of the time 4. Insomnia or hypersomnia nearly every day 5. Observed psychomotor agitation or retardation 6. Fatigue or loss of energy most of the time 7. Feelings of worthlessness or excessive or inappropriate guilt most of the time 8. Diminished ability to think or concentrate, or prominent indecisiveness most of the time 9. Recurrent thoughts of death, suicidal ideation

*In patients with significant dysfunction or a high level of distress in whom other factors (eg, drugs, medical conditions, bereavement) have been excluded. Source: Reference 11.

Table 3. Diagnostic Criteria for Melancholic Features of Depression

<p>A. Either of the following:</p> <ol style="list-style-type: none"> 1. Anhedonia (absence of pleasure from the performance of acts that would ordinarily be pleasurable) 2. Inability to temporarily feel better in response to pleasurable stimuli <p>B. Three or more of the following:</p> <ol style="list-style-type: none"> 1. Depressed mood distinctly different from sadness or grief 2. Depression worse in morning 3. Early morning awakening 4. Marked psychomotor agitation or retardation 5. Significant anorexia or weight loss 6. Excessive or inappropriate guilt

Source: Reference 11.

Concurrent medical illness is a major risk factor for suicide. About 70% of suicides occur in patients with a history of chronic disease.² For example, suicide rates in people with acquired immunodeficiency syndrome are 21 to 36 times greater than in the general population.¹⁵ Depression accompanying poor health may account for the fact that 25% of all suicides occur in elderly people.² Substance abuse and chronic pain or disability also increase the risk of suicide.

Treatment

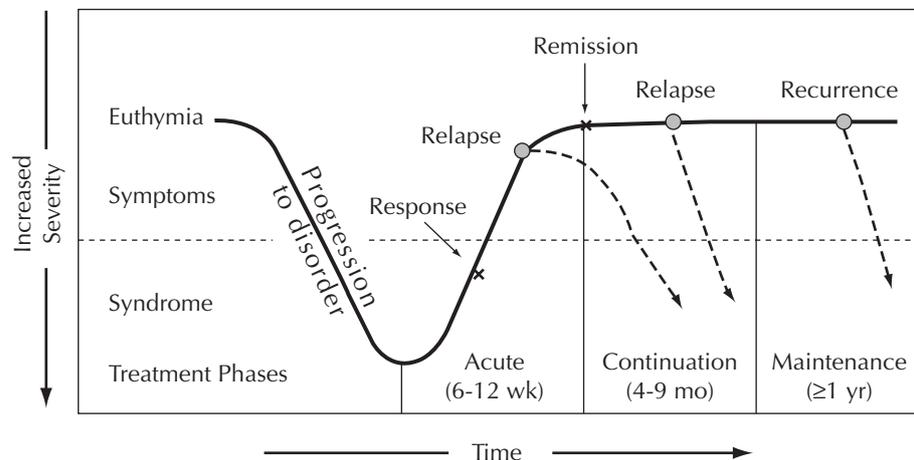
There are 3 phases of treatment for MDD (Figure).¹⁵ The *acute phase* of treatment begins when the patient first presents with an episode of depression, and the treatment goal is to elicit a response to medication or psychotherapy, or both.¹⁶ From a clinical perspective, this phase of treatment is most successful if it results in a remission rather than merely a response. Prevention of relapse or recurrence of the initial depressive episode is the best way to prevent depression-related morbidity. The *continuation phase* begins after symptoms have responded to acute

intervention.¹⁶ The goal during this phase is to prevent symptom relapse; once the patient is symptom free, remission is considered to have occurred. During the *maintenance phase*, the goal is to prevent a recurrence.¹⁶

Remission is said to have occurred when the individual becomes asymptomatic (ie, no longer meets the syndromal criteria for major depression and has no more than minimal symptoms). In clinical research, remission is defined as a Hamilton Rating Scale for Depression score of 7 or less.¹⁷ Remission may be the most relevant endpoint for clinicians.

Psychotherapy. The efficacy of psychotherapy for depression is difficult to ascertain because of the challenges in conducting research and evaluating results. Studies usually have involved a select population of motivated individuals with less severe forms of depression. Behavioral, cognitive, and interpersonal psychotherapies have all shown efficacy rates of 40% to 50%.² Some comparative studies have shown that psychotherapy is more effective than antidepressant drug therapy,² except in patients with melan-

Figure. Treatment Phases for Major Depressive Disorder



Source: Kupfer DJ. Long-term treatment of depression. *J Clin Psychiatry* 1991;52(suppl):28-34. Adapted with permission.

cholic depression, in whom response to medication is much better, although some evidence has shown equivalence between specific psychotherapies and medication. Generally, outcome is improved when antidepressant treatment and psychotherapy are combined, although definitive treatment has only recently been published.¹⁸

Psychotherapy should be considered a first-line treatment in less severe, uncomplicated, nonmelancholic cases, particularly if the patient prefers it to drug therapy or has had a positive response to previous psychotherapy, or if a patient prefers to have a course of psychotherapy first.

Pharmacotherapy. The objective of antidepressant pharmacotherapy is to reduce and ultimately remove all signs and symptoms of the depressive syndrome. Reduction and removal of symptoms not only benefit the patient, but also may reduce the cost burden on the healthcare system.

More than 24 antidepressant agents, which work by 7 different mechanisms (Table 4), are currently available on the US market. The classic mechanisms of action are those shared by monoamine oxidase inhibitors (MAOIs) and tricyclic antidepressants (TCAs). The 5 newer categories are: (1) selective serotonin reuptake inhibitors (SSRIs); (2) norepinephrine/dopamine reuptake inhibitors (NDRIs); (3) serotonin/norepinephrine reuptake inhibitors (SNRIs); (4) serotonin antagonist reuptake inhibitors (SARIs); and (5) noradrenergic and specific serotonergic antidepressants (NaSSAs). Regardless of the initial choice of pharmacotherapy, about 30% to 50% of patients do not respond to the initial medication.¹⁹

Classic Antidepressants: MAOIs and TCAs. The first antidepressants were discovered 40 years ago by serendipity. Only much later was it determined that these early agents worked either by inhibiting the enzyme MAO or by blocking the reuptake of norepinephrine and serotonin (5-hydroxytryptamine [5-HT]). Interestingly, no subsequent antidepressant can surpass

the classic agents in overall efficacy in clinical trials. However, the newer agents are far safer and better tolerated. The classic agents dominated the treatment of depression for almost 30 years, from the late 1950s until the late 1980s when the SSRIs were introduced.

The action of an MAOI is to increase the availability of the monoamine neurotransmitters norepinephrine, dopamine, and 5-HT by blocking their metabolism. The classic MAOIs are nonselective and irreversible, but the newer MAOIs are selective for MAO-A or MAO-B and are reversible (Table 5). Several reversible

Table 4. The 7 Classes of Antidepressants

<ul style="list-style-type: none"> ■ Monoamine oxidase inhibitors <ul style="list-style-type: none"> – Isocarboxazid – L-deprenyl (also known as selegiline) – Moclobemide (not available in the United States) – Phenelzine – Tranylcypromine ■ Tricyclic antidepressants <ul style="list-style-type: none"> – Amitriptyline – Chlordiazepoxide plus amitriptyline – Clomipramine – Desipramine – Doxepin – Imipramine – Maprotiline – Perphenazine plus amitriptyline – Protriptyline – Trimipramine ■ Selective serotonin reuptake inhibitors <ul style="list-style-type: none"> – Citalopram – Fluoxetine – Fluvoxamine – Paroxetine – Sertraline ■ Norepinephrine/dopamine reuptake inhibitors <ul style="list-style-type: none"> – Bupropion ■ Serotonin/norepinephrine reuptake inhibitors <ul style="list-style-type: none"> – Venlafaxine ■ Serotonin antagonist reuptake inhibitors <ul style="list-style-type: none"> – Nefazodone – Trazodone ■ Noradrenergic and specific serotonergic antidepressants <ul style="list-style-type: none"> – Mirtazapine
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inhibitors of MAO-A are in development, but only moclobemide is marketed (although not in the United States).

TCAs are actually 5 or more drugs in 1: (1) a serotonin reuptake inhibitor; (2) a norepinephrine reuptake inhibitor; (3) an anticholinergic-antimuscarinic drug (M_1); (4) an alpha-adrenergic antagonist; and (5) an antihistamine. They also inhibit sodium channels at overdose levels, causing potentially lethal cardiac arrhythmias and seizures.

The therapeutic actions of TCAs are thought to be a result of mostly norepinephrine reuptake inhibition. The exception is clomipramine, which has substantiated serotonin reuptake pump inhibition.

Most adverse effects associated with TCAs can be explained by their blockade of neurotransmitter receptors. Blockade of histamine receptors causes weight gain and drowsiness; M_1 (anticholinergic/antimuscarinic) blockade of acetylcholine receptors causes constipation, blurred vision, dry mouth, and drowsiness; α_1 blockade causes dizziness, decreased blood pressure, and drowsiness.

SSRIs (*Citalopram, Fluoxetine, Fluvoxamine, Paroxetine, and Sertraline*). The SSRIs are the most widely prescribed antidepressants in the United States, accounting for well over half of all antidepressant prescriptions.²⁰ Five different agents form the members of the SSRI

class. These agents have distinct chemical structures, secondary pharmacologic properties, and pharmacokinetics.

The SSRIs have revolutionized the treatment of depression for a number of reasons. The principal advantage of these drugs over the classic antidepressants (MAOIs and TCAs) is their much improved safety and tolerability. Whereas the classic antidepressant agents are lethal in overdose, the SSRIs are not. In addition, the cardiac toxicity and troublesome anticholinergic side effects are absent from the SSRIs. These agents, with their improved tolerability profile, arrived on the scene in the 1980s, just as new data demonstrated the value of long-term treatment in preventing relapse of future depressive episodes.²¹ Thus, long-term treatment is much more acceptable with the SSRIs than with the TCAs, and compliance is much greater.

Another advantage of the SSRIs is the breadth of their therapeutic profile, which extends far beyond antidepressant actions. SSRIs have proven efficacy in panic disorder, obsessive-compulsive disorder, and bulimia, with encouraging findings for treatment of social phobia, posttraumatic stress disorder, premenstrual dysphoric disorder, migraine, dysthymia, and many other conditions.

The mechanism of action of SSRIs usually is explained simply as selective inhibition of the serotonin transporter. More specifically, however, the therapeutic action of SSRIs is thought to result from delayed disinhibition of serotonin neurotransmission in at least 4 different key pathways.²² When an SSRI is administered, it immediately blocks the serotonin reuptake pump. However, this action causes a sudden increase in serotonin predominantly in the somatodendritic area, and not at the axon terminals where serotonin is presumably needed to exert therapeutic actions.

If SSRIs are administered chronically, the sustained increases of serotonin in the somatodendritic area of the serotonin neuron cause the somatodendritic serotonin-1A autoreceptors to desensitize. Once the somatodendritic serotonin

Table 5. Monoamine Oxidase Inhibitors (MAOIs)

<ul style="list-style-type: none"> ■ Classic MAOIs—irreversible and nonselective <ul style="list-style-type: none"> – Isocarboxazid – Phenelzine – Tranylcypromine ■ Reversible inhibitors of MAO-A <ul style="list-style-type: none"> – Moclobemide (not available in the United States) ■ Selective inhibitors of MAO-B <ul style="list-style-type: none"> – L-deprenyl (also known as selegiline)
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autoreceptors desensitize, neuronal impulse flow is no longer as readily inhibited by serotonin. Thus, neuronal impulse flow is “turned on.” Another way to characterize this action is that serotonergic neurotransmission is disinhibited, and more serotonin is released from the axon terminal. However, this increase is delayed compared with the increase of serotonin in the somatodendritic areas of the serotonin neuron. This delay is the result of the time it takes for somatodendritic serotonin to desensitize the serotonin-1A autoreceptors, and “turn on” (ie, disinhibit) neuronal impulse flow in the serotonin neuron. Again, this delay may account for why SSRIs do not relieve depression immediately. Finally, once SSRIs have blocked the reuptake pump, increased somatodendritic serotonin, desensitized somatodendritic serotonin-1A autoreceptors, disinhibited neuronal impulse flow, and increased release of serotonin from axon terminals, the final step is the desensitization of postsynaptic serotonin receptors.²² The ultimate target of all antidepressants may actually be the nucleus and gene expression.

Although the efficacy of SSRIs is broad, many clinicians believe that SSRIs are not as effective for severe depression as other agents with dual mechanisms such as TCAs, the SNRI venlafaxine, or the NaSSA mirtazapine. Moreover, SSRIs may produce bothersome side effects such as anxiety, sleep disturbances, panic attacks, sexual dysfunction, and gastrointestinal disturbances.

NDRIs (Bupropion). The only antidepressant to act selectively on the noradrenergic and dopaminergic systems is bupropion. This property renders the actions of bupropion to be unique not only from the SSRIs, but also from the other classes of antidepressants, all of which cause serotonergic interactions of one type or another.

When patients do not respond to or do not tolerate SSRIs, bupropion may be substituted because of its unique pharmacology, or added as an augmenting agent either

to amplify therapeutic effects or to eliminate side effects, particularly SSRI-induced sexual dysfunction. At full doses, bupropion can cause seizures at a rate of 0.4%, about the same as full-dose TCAs.²³

SNRIs (Venlafaxine, Venlafaxine Extended-Release). Venlafaxine is characterized by potent and selective inhibition of serotonin and norepinephrine reuptake at neuronal terminals. In con-

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trast to TCAs, venlafaxine has no significant binding affinity for histaminic, α_1 -adrenergic, or muscarinic cholinergic receptors. Venlafaxine also has no significant effects on monoamine oxidase. The rapid antidepressant response observed with venlafaxine is believed to be the result of the combined reuptake blockade of serotonin and norepinephrine.

After oral administration, venlafaxine reaches peak plasma concentration in 2 to 2.5 hours. Venlafaxine has an elimination half-life of about 5 hours, but the half-life of its active metabolite, O-desmethylvenlafaxine (ODV), is about 11 hours.²⁴ The ODV metabolite has a pharmacologic profile similar to that of venlafaxine itself. Venlafaxine is well absorbed; at least 92% of a single dose of venlafaxine is absorbed. Although administration with food slightly delays the absorption of venlafaxine, the total amount absorbed is unchanged.²⁴

Numerous clinical studies have demonstrated the antidepressant effica-

cy of venlafaxine (both immediate- and extended-release formulations) in the treatment of patients with MDD. In clinical trials, venlafaxine produced significantly greater improvements in total scores of several depression rating scales versus placebo. In comparative trials, the efficacy of venlafaxine was comparable to that of clomipramine, imipramine, trazodone, and fluoxetine. The onset of antidepressant action of venlafaxine is about 2 to 4 weeks after the initiation of therapy. Long-term treatment with venlafaxine is well tolerated. The drug does not appear to affect psychomotor performance.

Therapy with venlafaxine has been shown to be cost effective. In 1 analysis that used the results from a study of 67 hospitalized depressed patients, venlafaxine was estimated to result in a cost savings of 11.3% versus fluoxetine.²⁵ Venlafaxine is the first medication to be approved by the US Food and Drug Administration for use in both MDD and generalized anxiety disorder; therefore, it is an appropriate first-line choice for the monotherapy of patients with depression and comorbid anxiety.

SARIs (Nefazodone). Nefazodone blocks the 5-HT₂ receptors in contrast to SSRIs, which stimulate these receptors. Thus the therapeutic and side-effect profiles of nefazodone and SSRIs differ. Perhaps the biggest difference is that nefazodone quickly reduces anxiety and insomnia, whereas SSRIs may cause short-term increases in those conditions. In addition, 5-HT₂ receptor blockade may not increase the incidence of akathisia or sexual dysfunction nearly to the degree that 5-HT₂ receptor stimulation does.

NaSSAs (Mirtazapine). Mirtazapine has both adrenergic and serotonergic actions, and its serotonergic actions are selectively directed to the 5-HT_{1A} receptor because the 5-HT₂ and 5-HT₃ receptors are blocked. The adrenergic and serotonergic actions are a result of its α_2 -agonist properties.²⁶

The α_2 antagonism disinhibits both serotonin and norepinephrine neurotransmission. Because mirtazapine has 5-HT₂ antagonist properties, its profile changes from that of an SSRI to that of other 5-HT₂ antagonists such as nefazodone. Because mirtazapine is also a 5-HT₃ antagonist, it does not share the actions of SSRIs that lead to 5-HT₃ stimulation. Thus, mirtazapine is not associated with the gastrointestinal disturbances caused by SSRIs. Mirtazapine has strong antihistamine properties, which explains its side effects of weight gain and sedation.²⁷

Electroconvulsive Therapy. Electroconvulsive therapy (ECT) is considered by many experts to be the most effective intervention available for depression, particularly the more severe forms (ie, imminent suicide, melancholia, and psychotic depression). The treatment is safe, even in medically compromised and elderly patients.²⁸ Use of ECT does not preclude pharmacotherapy. Although ECT induces remission of the depression, the duration of the effect is limited; therefore, treatment with antidepressant drugs is required to prevent relapse over the long term. Complications can occur, including the potential dangers of general anesthesia and transient memory dysfunction.

Managed Care Perspectives

Depression is a common illness, and antidepressants are among the most frequently prescribed classes of medication on health maintenance organization (HMO) formularies.²⁹ A midwestern managed health plan (Healthsource of Indiana) examined the use of antidepressants as part of a quality-improvement program.⁴ The impetus for this study was the observation that antidepressants consistently ranked among the top 3 classes of drugs prescribed over a 24-month period and constituted the most costly drug class for the plan. Nearly 50% of patients who received a prescription for antidepressants remained on the drugs for fewer than 30 days, suggesting profound underusage of the drugs.⁴

Identifying and appropriately treating patients with depression has important implications for health plans. Patients with depression use healthcare services more frequently than those without depression.⁴ Furthermore, depressed patients cost almost twice as much to treat as nondepressed patients.^{30,31} Failure to diagnose and appropriately treat depressed patients results in increased healthcare utilization and costs. In addition, depressed patients who are undertreated or inappropriately managed may suffer loss of productivity and a diminished quality of life (QOL).³² Identifying and treating these high users of medical care with a structured program was found to be more effective than usual care.³³

Antidepressant Utilization Patterns.

Most antidepressants are prescribed by PCPs. A 31-plan national managed care organization (MCO) recently reported that 77% of all antidepressant prescriptions are written by PCPs.¹ It has been suggested that most patients with depression can be managed effectively by PCPs, and that only a small proportion of patients require referral to a psychiatrist.³⁴ However, previous studies have suggested that PCPs misdiagnose depression in as many as 2 of 3 cases.³⁵ Even when the correct diagnosis of depression is established, patients are often treated with subtherapeutic doses of antidepressants over periods of time insufficient to produce clinical benefit.³⁶

Healthsource of Indiana identified the indications documented by PCPs for prescribing antidepressants and examined follow-up documentation for patients who received an antidepressant prescription.⁴ Records of 3037 patients who were prescribed an antidepressant medication in the primary care setting during an 18-month interval were randomly reviewed until a sample of 100 was reached. Seventy percent of the charts documented 1 or no symptoms (based on criteria established by the American Psychiatric Association¹¹) of major depression, whereas 90% con-

tained documentation of 3 or fewer symptoms.⁴ Furthermore, use of screening tools was documented in only 4% of charts, and only 57% of charts indicated a scheduled depression-focused follow-up visit. Interestingly, compliance with the prescribed medication regimen was substantially better among patients who had a scheduled follow-up visit than among those who did not. Documentation regarding outcome indicated symptomatic improvement in only 37% of the records. Only 16%

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of patients in the sample were referred to a psychiatrist.

These data strongly suggest not only a lack of precision in the diagnosis of depression on the part of PCPs, but also an overall management scheme that is profoundly suboptimal. Based on these results, the study investigators suggested 4 immediate steps for quality improvement: (1) improvement in documentation; (2) enhanced use of screening tools; (3) increased use of patient education materials detailing the side effects and delay in onset of clinical benefits associated with antidepressants; and (4) mandatory scheduling of follow-up visits.⁴ The high prevalence and enormous socioeconomic impact of depression necessitate efficient and effective treatment approaches.

The PCP plays an important role in the treatment of depression. Patients often present first to their PCP with somatic complaints. Therefore, the PCP plays a significant role in initial screen-

ing and identification of depression and comorbid conditions. Early intervention and aggressive treatment may prevent future disabling depressive episodes. Moreover, increased recognition and appropriate management may reduce the morbidity and mortality related to MDD.

Comorbidity. The importance of accurate diagnosis and appropriate management of depression becomes even more important when taking into account the observation that depression tends to occur in association with a large number of comorbid conditions including anxiety, other mood disorders, substance abuse disorders, and a host of medical conditions ranging from diabetes to heart disease, stroke, and cancer.³⁷⁻⁴¹ Whereas the rate of MDD among people in the community is estimated to be between 2% and 4%, among primary care patients the rate is between 5% and 10%, and among medical inpatients it is in excess of 10%.³⁹ The recognition and treatment of comorbid depression may not only improve the outcome of the underlying medical condition, but also may improve functional status, enhance QOL, and decrease healthcare utilization.

In patients with coronary heart disease and no history of myocardial infarction, 18% to 20% may experience depression.³⁷ Furthermore, in patients with coronary heart disease who had a history of myocardial infarction, the prevalence of depression was estimated to be 40% to 65%.³⁷ Depression can contribute to a worsening of symptoms and to poor adherence to cardiac treatment regimens. Patients who survive heart attacks but have major depression have a 3 to 4 times greater risk of dying within 6 months than those without depression.^{37,42}

Of the 600,000 Americans who experience a first or recurrent stroke each year, an estimated 10% to 27% have major depression.³⁸ An additional 15% to 40% experience depressive symptoms within 2 months after the stroke.³⁸ Seventy-five

percent of strokes occur in people 65 years of age and older. With stroke being a leading cause of disability in older people, proper recognition and treatment of depression in this population is particularly important.³⁸

Major depression is particularly common in people with diabetes and in those with cancer.^{39,40} A higher than average co-occurrence of depression with other psychiatric disorders, such as anxiety and eating disorders, has also been documented.⁴¹ Concurrent depression is present in 13% of patients with panic disorder; in about 25% of these patients, the panic disorder preceded the depressive disorder. Between 50% and 75% of patients with eating disorders have a lifetime history of MDD.⁴¹

Comorbid depression is associated with an increased risk of disability in activities of daily living, physical health status, and cognitive functioning.⁴³ Moreover, if disability does occur, it may exert a downward-spiral effect by further exacerbating depressive symptoms and physical health. Given the importance of activities-of-daily-living functioning on QOL and utilization of medical services, recognition of depressive symptoms should be considered a crucial point of intervention.

Depression and the Workplace. The relationship between depressive symptoms, satisfaction with healthcare, and 2-year work outcomes was examined in a national cohort of employees.⁴⁴ A total of 6239 employees of 3 major corporations completed surveys on health and satisfaction with healthcare in 1993 and 1995. This study used bivariate and multivariate analyses to examine the relationships between depressive symptoms, satisfaction with healthcare in 1993, and work outcomes in 1995. The odds of missed work as a result of health problems in 1995 were twice as high for employees with depressive symptoms in both 1993 and 1995 as for those without depressive symptoms in either year. The odds of decreased effectiveness at work in 1995 were 7 times as high in

depressed employees as in nondepressed employees.⁴⁴

Employers are playing an increasingly influential role in determining the scope and character of healthcare coverage in the United States. A study performed by Druss et al⁴⁵ examined the health and disability costs of depressive illness with those of 4 other chronic conditions among employees of a large US corporation. Data from the health and employee files of 15,153 employees who filed health claims in 1995 were examined. Analyses compared the mental health costs, medical costs, sick days, and total health and disability costs associated with depression and heart disease, diabetes, hypertension, and back problems. Regression models were used to control for demographic differences and job characteristics. Employees treated for depression incurred annual per capita health and disability costs of \$5415, significantly more than the cost for hypertension and comparable to the cost for each of the other 3 medical conditions. Healthcare costs for employees with depressive illness plus any of the other conditions were 1.7 times more than those with the comparator medical conditions alone. Depressive illness was associated with a mean of 9.86 annual sick days, significantly more than any of the other conditions. Depressed employees younger than 40 years of age took 3.5 more annual sick days than those 40 years old or older. The authors concluded that the cost of depression to employers, particularly in lost workdays, is as great or greater than the cost of many other common medical illnesses, and the combination of depression and other common illnesses is particularly costly.⁴⁵

In a secondary analysis of data from a community epidemiologic survey conducted at 7 primary care clinics of a Seattle-area HMO (Group Health Cooperative of Puget Sound), clinical outcomes, employment status, and workdays missed because of illness were examined.⁴⁶ Medical comorbidity was assessed using computerized pharmacy data, and

medical costs were assessed using the HMO's computerized accounting data. Patients were classified as remitted (41%), improved but not remitted (47%), and persistently depressed (12%).⁴⁶ After adjustment for depression severity and

The cost of depression to employers, particularly in lost workdays, is as great or greater than the cost of many other common medical illnesses, and the combination of depression and other common illnesses is particularly costly.

medical comorbidity at baseline, employees with greater clinical improvement were more likely to maintain paid employment ($P = .007$) and reported fewer days missed from work ($P < .001$). Employees with better 12-month clinical outcomes had marginally lower healthcare costs during the second year of follow up ($P = .06$).⁴⁶ These longitudinal results suggest that recovery from depression is associated with significant reductions in work disability and possible reductions in healthcare costs.

Depressive disorders in the workplace persist over time and have a major detrimental effect on work performance. Based on studies that have examined the effects of depression in the workplace, there appears to be an important link between an employee's perceptions of clinical care and work outcomes. Moreover, absenteeism may represent only a small fraction of the cost of depression in the workplace.

Depression and the Health Plan Employer Data and Information Set. The National Committee for Quality

Assurance (NCQA), a nonprofit group, has developed an accreditation program that uses established standards to rate a health plan's overall performance. Health plans are seeking NCQA accreditation as a means of documenting quality and quality improvement. The Health Plan Employer Data and Information Set (HEDIS) is a set of more than 60 performance measures that addresses key areas of interest identified by employer representatives. The most important of these measures is quality of care. HEDIS is the first comprehensive attempt to make health plans directly comparable and accountable for their performance. HEDIS is emerging as the gold standard on which to base report cards for managed health plans. In doing so, it will likely play an enormous role in determining how PCPs function.

The first, most comprehensive, and most intensive focus of NCQA review is an MCO's own internal quality assurance system. To meet NCQA standards, a health plan must have a comprehensive quality improvement program accountable to its highest organizational levels. The program's scope and content must be broad and able to cover the full spectrum of services included in its delivery system. In addition, the program should focus on important aspects of care and service. Clinical issues that have a major impact on the health status of plan members, such as depression and comorbid depression, should be addressed.

The HEDIS measure for depression is "Antidepressant Medication Management."⁴⁷ This measure gauges the percentage of long-term adherence to a prescribed medication regimen among plan members with depression. The most recently reported results of the HEDIS Antidepressant Medication Management measure have indicated a lack of long-term treatment adherence.⁴⁷ The mean for all plans reporting for the percentage of patients who follow up with a physician after the diagnosis of depression was 21%. The mean percentage of patients participating in active phase treatment (0 to 84 days after diagnosis) was 59%. The

mean percentage of patients participating in continuation phase treatment (85 days to 6 months after diagnosis) was 42%.⁴⁷ If the health plans in the sample can be considered a microcosm of health plans nationwide, then clearly, better recognition and management of depression is needed.

Conclusion

Depression is a costly illness in terms of both human suffering and societal impact. Improvements in patient care and resource utilization can be expected to occur through better recognition of the disorder, initiation of appropriate treatment early in the course of the condition, careful monitoring of treatment to ensure remission, and the use of medications with good tolerability and safety profiles.

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