Strategies for Managing Depression Complicated by Bipolar Disorder, Suicidal Ideation, or Psychotic Features

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Background: **Major depression, a common clinical problem that, if recognized early and treated vigorously, is often highly responsive to antidepressants and can be complicated by such features as mania, suicidal thoughts and actions, and psychosis. Suicide is one of the most serious complications of major depression.**

Methods: **An online search of the medical literature was used to select English-language articles addressing depression using, but not limited to, the following specific terms: "primary care," "depressive disorders," "bipolar disorder," "suicide," "psychosis," and "antidepressants."**

Results and Conclusions: **Treatment of the manic phases of bipolar disorder includes lithium or anticonvulsants. Breakthrough depression can be particularly resistant to treatment in bipolar patients, and the tricyclic antidepressants can cause patients to cycle more rapidly into the manic phase. The selective serotonin reuptake inhibitors (SSRIs) and bupropion are less likely to cause rapid cycling in bipolar disorder. Depressed patients with suicidal tendencies should be closely monitored and given full doses of antidepressant medications. The SSRIs lessen suicidal tendencies and, importantly, are markedly safer than the tricyclic antidepressants when taken in an overdose. Depressed patients can also become psychotic, exhibiting mood-congruent delusions. Combination therapy with antidepressant and antipsychotic medications is often necessary. Some physicians prefer to hospitalize patients with psychotic depression. Depression can be a complex and multifaceted disorder that requires careful diagnosis and treatment plans. (J Am Board Fam Pract 1996;9:261-9.)**

Depression is a common, but multifaceted, disorder that is frequently encountered in a primary care practice. It is important, therefore, for the primary care physician to be knowledgeable about the diagnosis and management of the depressive disorders. The usual clinical signs and symptoms and management of depressed patients can be complicated by bipolar disorder, suicidal ideation, or psychotic features (Table 1). This article addresses ways to recognize depression and care for these patients.

Methods

An online, bibliographic search (MEDLINE) of the medical literature from 1966 to the present was used to select clinical studies, case reports, and review articles. Only English-language publications were reviewed. Specific terms included, but were not limited to, "depressive disorders," "bipolar disorder," "suicide," "psychosis," and "antidepressants." Additional articles were cross-referenced from textbooks and from the bibliographies of articles found by the search.

Depression in Primary Care

The Epidemiologic Catchment Area study conducted by the National Institute of Mental Health in the early 1980s found that mental disorders affect approximately 22 percent of the US population in a 1-year period, making mental disorders as prevalent as cardiovascular disease.[1] Nearly one half of all patients with mental disorders are cared for in nonpsychiatric settings, namely, by a primary care physician.[2] Among the mental disorders, major depression is probably the most common medical or psychiatric disorder seen by primary care physicians.[2,3] Bipolar disorder is another affective mental illness seen in pri-

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Table 1. Clinical Features of Major Depression, Bipolar Depression, and Psychotic Depression.

Affective Disorder	Distinguishing Features	Suicidal Tendencies
Major depression (unipolar depression)	Depressed mood or loss of interest or pleasure in activities for at least 2 weeks	Common
Bipolar depression	Abnormally and persistently elevated, expansive, or irritable mood (ie, mania) lasting at least 1 week. Manic episodes alternate (cycle) with depressive episodes	Common
Psychotic depression	Depression with mood-congruent delusions, such as guilt, deserved punishment, nihilism, somatization, or poverty. Delusions are more common than hallucinations	Common

mary care. In any given year, 10.3 percent of adults have major depression, and 1.3 percent have bipolar disorder (ie., manic-depressive illness).[4] Of the depressive disorders, psychotic depression is one of the most difficult-to-manage subtypes. It is therefore important for primary care physicians to be able to recognize and provide initial management for this disorder.

The importance of recognizing and treating depression is underscored by the mortality associated with this disorder. Suicide, which usually results from depression or other mood disorders, is the ninth leading cause of death in the United States.[5] The suffering that results from depression extends well beyond the suicide statistics, however, for it exacts a severe toll in the daily lives of those with affective disorders. For example, patients who are depressed or have depressive symptoms experience poorer physical function, more perceived pain, and a greater number of days spent in bed than those who have diabetes mellitus, arthritis, or hypertension.[6] In addition, patients with bipolar disorder have impairments in all areas of functioning, even when their symptoms are controlled.[7,8]

Because of the importance and prevalence of these disorders, primary care physicians need to develop expertise in the diagnosis and management of depression.[9,10] Recognizing that a patient is depressed is the first step. Unfortunately, depression has often been underdiagnosed, perhaps because primary care physicians tend to recognize depression mainly by the degree of distress the patient exhibits rather than by noting the symptoms of depression.[3] Although primary care physicians have been criticized for inadequately treating depressed patients,[11] a recent study indicates that their approach to depression has been improving.[12]

Primary care physicians can also miss the diagnosis because depressed patients often complain of physical symptoms or anxiety rather than sadness or depression. In the course of a busy practice with limited time for each patient, the subtle manifestations of depression can understandably be missed. Thus, the physician needs to have a low threshold of suspicion for depression because it is such a common and serious disorder. This paper aims to enhance the ability of primary care physicians to care for depressed patients by providing information about the management of depression in the setting of selected comorbid psychiatric conditions.

Bipolar Disorder

Bipolar disorder is the term used in the *Diagnostic and Statistical Manual of Mental Disorders, 4th Edition* (DSM-IV),[13] which replaces the older term, manic-depressive disorder. This affective disorder is characterized by recurrent, cycling episodes of depression and mania (type I bipolar disorder) or depression and hypomania (type II bipolar disorder). A history of at least one episode of mania (Table 2) is necessary to make a definite diagnosis of type I bipolar disorder. The diagnosis of type II bipolar disorder is made when patients have recurrent depression and at least one episode of hypomania. Bipolar disorder may be suspected, however, when a patient is depressed, especially if the depression is recurrent, and has a family history of bipolar disorder. Patients do not always volunteer a history of mania or hypomania, and the physician needs to ask explicitly.[14]

Typically, bipolar disorder begins during adolescence or young adult life with a median age of onset of 19 years.[15,16] This diagnosis should be suspected in a depressed adolescent if the depression is characterized by an acute onset or occurs in conjunction with hypersomnia, psychomotor retardation, or psychosis.[17] Bipolar disorder can

easily be confused with secondary mania, which results from organic illness, medications, or substance abuse. Secondary mania should be suspected if the initial manic episode occurs in a prepubertal child or in an adult older than 40 years.[18]

Although challenging, treatment of bipolar disorder is extremely important. Patients with bipolar disorder have high mortality rates from both suicide and natural causes, especially cardiovascular disease and hypertension.[19] Furthermore, there is evidence that mania or depression might destroy brain tissue, leading to cognitive impairment, particularly in male patients and the elderly.[16] Bipolar disorder seriously disrupts patients' lives and results in greatly impaired emotional, social, and occupational performance.

Although pharmacotherapy is the cornerstone of treatment of bipolar disorder, adjunctive psychotherapy is often useful and can enhance compliance with prescribed medications, decrease hospitalizations, and improve family and social functioning.[20] The type of psychotherapy depends upon comorbid conditions, the patient's desires, and available resources. If a patient has a marked character disorder, formal psychotherapy by a trained therapist might be indicated. For many patients, however, supportive therapy is appropriate and can be provided by an interested primary care physician.

Table 2. Diagnostic Criteria for a Manic Episode.

A. A distinct period of abnormally and persistently elevated, expansive, or irritable mood, lasting at least 1 week (or any duration if hospitalization is necessary)

B. During the period of mood disturbance, three (or more) of the following symptoms have persisted (four if the mood is only irritable) and have been present to a significant degree:
   1. Inflated self-esteem or grandiosity
   2. Decreased need for sleep (eg, feels rested after only 3 hours of sleep)
   3. More talkative than usual or pressure to keep talking
   4. Flight of ideas or subjective experience that thoughts are racing
   5. Distractibility (ie, attention too easily drawn to unimportant or irrelevant external stimuli)
   6. Increase in goal-directed activity (either socially, at work or school, or sexually) or psychomotor agitation
   7. Excessive involvement in pleasurable activities that have a high potential for painful consequences (eg, engaging in unrestrained buying sprees, sexual indiscretions, or foolish business investments)

C. The symptoms do not meet criteria for a mixed episode of major depression or mania

D. The mood disturbance is sufficiently severe to cause marked impairment in occupational functioning or in usual social activities or relationships with others, or to necessitate hospitalization to prevent harm to self or others, or there are psychotic features

E. The symptoms are not due to the direct physiological effects of a substance (eg, a drug of abuse, a medication, or other treatment) or a general medical condition (eg, hyperthyroidism)

From the American Psychiatric Association.[14]
Note: Manic-like episodes that are clearly caused by somatic antidepressant treatment (eg, medication, electroconvulsive therapy, light therapy) should not count toward a diagnosis of bipolar disorder.

Lithium

Lithium remains the mainstay of acute and prophylactic pharmacotherapy for bipolar disorder. Doses of 300 mg two or three times daily should be administered to maintain serum concentrations of 0.8 to 1.0 mEq/L.[16]

Some patients are able to take the daily amount in one dose. When tolerated, a once-daily regimen will enhance compliance. Onset of response during an acute manic episode is 5 to 10 days or longer, so many physicians also prescribe a brief course of a benzodiazepine or neuroleptic to control symptoms until therapeutic lithium serum concentrations are achieved. Lithium therapy causes many side effects, including excessive thirst, polyuria, confusion, poor concentration, mental slowness, memory problems, fine hand tremor, weight gain, drowsiness, and diarrhea (Table 3), which might limit patient acceptance of therapy. In addition, potentially serious toxicity involving the gastrointestinal, hematologic, cardiovascular, renal, endocrine, nervous, and developing fetal systems requires that physicians monitor patients closely during treatment and consider carefully any underlying medical illness.[21,22] Many primary care physicians seek a psychiatric referral for manic patients who need lithium, particularly during an acute episode.

Bipolar disorder requires long-term pharmacotherapy. Generally, patients should be on lithium therapy for at least 5 years. Patients who are free of breakthrough mania or depression for at least 5 years while on lithium therapy are candidates for discontinuation. When a decision is made to stop lithium, dosages should be gradually tapered during a period of 4 weeks.[20-23] Patients with bipolar disorder are more likely to have a refractory manic episode when lithium is stopped abruptly.

Table 3. Early-Onset and Chronic Side Effects of Lithium Therapy.

Side Effects	Percent
Early-onset side effects (prevalence)	
Polyuria	50
Polydipsia	50
Tremor	47
Muscle weakness	33
Gastrointestinal disturbances	30
Side effects occurring during long-term therapy (prevalence)	
Neurologic	
Tremor, decreased concentration impaired memory, cogwheel rigidity	< 10
Renal	
Nephrogenic diabetes insipidus	12
Nephrotoxicity	Uncommon
Cardiovascular	
Nonspecific T-wave changes	20-30
Increased premature ventricular contractions	Uncommon
Thyroid	
Hypothyroidism	3-30
Increased thyroid-stimulating hormone levels	15
Hematologic	
Leukocytosis	30-45
Dermatologic	
Acne, psoriasis, alopecia, rash	Uncommon
Weight gain	25

From Kinney-Parker and Frankhauser.[70]

Although lithium has proven benefit in the treatment of mania, its antidepressant effects are often inadequate.[14-16] Roughly one third of patients develop breakthrough depression while on lithium, and treatment refractoriness is a major management problem in bipolar disorder.[24] A variety of strategies have been developed for patients who do not respond fully to lithium. Several anticonvulsant medications possess antimanic and antidepressant activity and have assumed a role in the treatment of bipolar disorder. In addition, the traditional antidepressants are also useful for patients with breakthrough depression.

Anticonvulsants

Carbamazepine, which is chemically similar to the tricyclic antidepressants and is believed to reduce kindling in the central nervous system (CNS),[25] was the first beneficial anticonvulsant for bipolar patients. Carbamazepine is more effective as an antidepressant than lithium[24] and is especially effective if the depression is severe, there is a history of discrete episodes of depression, or the depression is not chronic.[26] The target serum level for carbamazepine is approximately 10 µg/mL, but dosing should be titrated against side effects, and a more reasonable serum level range is 4 to 12 µg/mL. Dizziness, ataxia, diplopia, rash, and sedation are associated with carbamazepine therapy. Aplastic anemia and agranulocytosis occurs rarely. Carbamazepine is also a potent inducer of hepatic enzyme function, which with continued therapy will increase its own metabolism. Thus, frequently monitoring carbamazepine plasma concentrations might be necessary to avoid a diminished response. In addition, carbamazepine will also increase the metabolism and decrease the pharmacologic response of concomitantly administered drugs that are metabolized hepatically. Physicians should be aware that an antidepressant response for carbamazepine usually takes about 2 weeks, as is true of the classic antidepressants. Nevertheless, carbamazepine is a better antimanic agent than an antidepressant.[25,26]

Valproate is another anticonvulsant that has more recently been helpful in bipolar patients. Hepatic failure is a rare but serious complication of valproate therapy that necessitates liver function testing. Unlike carbamazepine, which has some antidepressant properties, valproate is primarily an antimanic agent.[20] It does decrease episodes of depression, but only in type II bipolar disorder.[24] Clonazepam also possesses antimanic activity, but it is not an effective antidepressant.[24] Although these anticonvulsants can be used alone for treatment of bipolar disorder, they can also be combined with lithium for additional effect. Combination therapy might be necessary in treatment-resistant patients who have rapid cycling, persistent depression, or an abnormal electroencephalogram (EEG).[27]

Antidepressants

Despite the prophylactic use of lithium or an anticonvulsant, patients might experience breakthrough depression. In such cases standard antidepressants can be temporarily added to the regimen. Any antidepressant can be used for this purpose, but some have certain advantages.[16-20] Selective serotonin reuptake inhibitors (SSRIs) can be superior to the tricyclic antidepressants and have a more tolerable side-effect profile.[14] Patients with atypical depression, especially if they

are resistant to tricyclic antidepressants, have been found to benefit from taking monoamine oxidase inhibitors (MAOIs).[14,24,28] Physicians, however, might prefer to prescribe an SSRI for these patients because of the obligatory dietary and medication restrictions of MAOI therapy. In addition, there are theoretical reasons why SSRIs can be beneficial in bipolar depression, as serotonin enhancement has been found to be therapeutic in this subclass of depressed patients.[24]

One potential side effect of antidepressants in patients with a bipolar disorder is a switch to mania or hypomania. Although there is some controversy about this switch process,[29,30] good evidence exists that it does occur and that the antidepressant might also cause an increased cycling rate and more mixed episodes (both manic and depressive symptoms).[20,26,31,32] Although the switch process is believed to occur with all antidepressants, it is less likely to occur with SSRIs or with bupropion than with the tricyclic antidepressants.[14,33] There are also case reports that describe manic switching upon discontinuation of antidepressants, including tricyclic antidepressants, trazodone, and MAOIs.[34]

When antidepressants are used for breakthrough depression in a patient with bipolar disorder, they should be prescribed as in the treatment of unipolar depression in full therapeutic doses for a full course of therapy. Antidepressant therapy in this setting should last approximately 6 to 9 months after the symptoms are controlled. Adding antidepressants to lithium to prevent recurrent episodes of depression is no more effective than lithium by itself.[24,35]

Patients who do not respond to an adequate trial of antidepressant therapy are candidates for psychiatric referral. The psychiatrist might recommend a variety of treatment strategies, including augmentation with thyroid hormone. Combination therapy with antidepressants or electroconvulsive therapy are other options that are often highly effective in either mania or depression.[16,24] For selected patients, primarily those with a seasonal pattern, light therapy may be recommended using 2500 lux for 2 hours per day.[20]

The Suicidal Patient

The lifetime prevalence of suicide in the general population is approximately 2.9 percent.[36] There has been an increasing incidence of suicide in the United States since 1970, which is thought to be due to increasing occurrence of depression and substance abuse, primarily among young adults.[37] At the highest risk of suicide are elderly white men, with a prevalence of 45 per 100,000 population.[38] Suicide is generally considered by an individual to be a solution to an unbearable life situation. Most of the time it results from the miserable mood and feeling of hopelessness that can accompany depression. When the depression is successfully treated, the suicidal ideation almost always abates.

Although women attempt suicide three times more often than men, men successfully complete suicide three times more often than women.[5] Risk factors for suicide include depression, panic disorder, substance abuse, advanced age, white race, social isolation, and underlying medical illnesses, such as AIDS.[39-41] Patients with schizophrenia are at high risk for successful suicide attempts, especially when they are depressed and feel hopeless, because they are more likely to use violent means such as a gun.[42,43]

Evaluation of suicidal tendencies begins with asking patients at risk whether they have suicidal ideation. If the patient has a plan, has taken some action, such as stockpiling pills or acquiring a handgun, or intends to use violent means, the patient is at high risk. Such actively suicidal patients should probably be referred to a mental health professional.[44] The risk of suicide increases if the patient feels hopeless, has attempted suicide in the past, has a family history of suicide, or has experienced a major negative life event.[45,46]

Even with searching for risk factors and evaluating the patient's intent, it is not possible to predict suicide accurately.[47] All the primary care physician can do is assess the patient's frame of mind as best as possible and make a reasonable judgment. High-risk patients will generally need hospitalization. Most family physicians will also prefer to co-manage these patients with a mental health professional or refer the patient to a psychiatrist until the suicidal ideation has resolved. If a nonpsychiatric mental health professional is involved, the family physician will need to provide antidepressants and evaluate the patient for any organic illness that could cause or complicate the depression. Nevertheless, some suicidal patients can be successfully cared for as outpatients. The physician should encourage the patient to enter

into a "no suicide" contract in which the patient agrees to notify the physician if the suicidal ideation gets worse and promises not to act on suicidal urges. This approach is often quite helpful.[41]

In addition to protecting the patient when necessary, the most important intervention the physician can undertake is to provide hope and aggressive treatment of the underlying cause. Usually, the cause is major depression with or without substance abuse. Patients should be treated with full doses of antidepressants in an effort to relieve the depression as rapidly as possible. The importance of adequate antidepressant therapy has been shown in several studies in which suicide victims were treated with subtherapeutic doses of antidepressants or were treated with only an antianxiety agent or psychotherapy.[42,43,48]

Supportive psychotherapy, cognitive psychotherapy, or interpersonal psychotherapy, in conjunction with involved family members, is important, particularly during the initial stage of treatment before the antidepressant response is achieved. This combined approach will provide the greatest protection against suicide. The primary care physician can provide supportive psychotherapy; cognitive or interpersonal psychotherapy will require a referral. Crumley[49] has outlined the following approach designed for primary care physicians: clarify issues, provide stress management, and assist the family.

The SSRIs offer clear-cut advantages for the suicidal patient. Of primary importance is their greater safety; SSRIs are less lethal when a patient deliberately overdoses.[50] In contrast, a lethal dose of a tricyclic antidepressant can be as low as 2000 mg, which is less than a 1-week supply of imipramine at 300 mg/d. Patients with suspected suicidal tendencies should never be prescribed more than a 1-week supply of any tricyclic antidepressant.

The SSRIs also might have another advantage over the tricyclic antidepressants in suicidally depressed patients. Mann and Kapur[51] have suggested that patients' suicidal tendencies improve during the first 2 weeks on SSRIs as compared with tricyclic antidepressants, a difference that disappears after 6 weeks. The reason for this possible earlier onset of response is unknown, but could be due to suicidal patients having decreased central serotonergic function, and SSRIs act selectively on the serotonin system.[52,53]

The benefit of the SSRIs in suicidally depressed patients stands in contrast to earlier concerns that SSRIs might actually increase suicidal ideation.[54] A meta-analysis of 17 double-blind studies has shown that there is no increased incidence of suicide during fluoxetine therapy when compared with tricyclic antidepressants.[55] Similarly, a review of the paroxetine clinical database revealed that patients did not become suicidal after beginning therapy. The incidence of suicide among patients prescribed paroxetine was 2.8 times lower than it was among those prescribed antidepressants (mainly tricyclic antidepressants) and 5.6 times lower than among those taking a placebo.[56] Clearly, then, the SSRIs are not associated with treatment-emergent suicidal tendencies. In fact, existing suicidal thinking will improve and often resolve during antidepressant therapy with an SSRI.

When primary care physicians are taught to recognize and manage depression and suicide, they are able to assess suicidal patients appropriately and reduce the incidence of successful suicide.[42,57] Even when a patient commits suicide, however, family members want their family physician to contact them and help them cope with the loss of their family member.[58]

Major Depression with Psychotic Features

Psychosis can complicate a major episode of either unipolar or bipolar depression. Major depression with psychotic features is defined as major depression with delusions or hallucinations, although delusions are more common.[59] Typically the delusions are mood congruent and concern guilt, deserved punishment, nihilism, somatic complaints, or poverty.[13] Severe psychomotor retardation or excitation strongly suggests a psychotic component and should alert the physician to search for accompanying delusions or hallucinations.[60]

Patients with a major depressive disorder that is severe and has psychotic features can have either mood-congruent or mood-incongruent delusions.[13] In the past mood-incongruent delusions were believed to suggest another form of psychosis, such as schizophrenia, but this distinction has not prevailed.[60] The diagnosis of major depression, severe with psychotic features, is made by recognizing the symptoms of depression. A history of depression or a family history of depression is very helpful in making the diagnosis.

Schizophrenia is considered to be a disorder distinct from the affective disorders, although there is some controversy about this distinction.[61,62] For example, it might not be possible to distinguish whether a psychotic episode is due to schizophrenia or bipolar disorder. The key to making the distinction is to follow the course of the depression over time and to note the family history. Sometimes distinguishing between them remains impossible, so a diagnosis of schizoaffective disorder is made.[13]

Patients who are prone to major depression with psychotic features tend to have psychotic episodes on more than one occasion. Thus, an elderly patient with no history of psychotic depression who has symptoms of psychotic depression should be examined for structural brain abnormalities.[59,63] Depression after stroke is common, for example, and if there is diffuse cerebral injury, especially to the right hemisphere, paranoid delusions can accompany the depression.[64] On the other hand, a young patient with new onset psychotic depression more likely has a bipolar disorder.[17,65]

Psychotic depression is a severe form of depression and requires vigorous treatment. Pharmacotherapy for psychotic depression requires aggressive dosing, careful drug titration, and often a combination of an antidepressant and an antipsychotic.[35] Combining the two medications is clearly superior to prescribing either singly; however, the clinician needs to monitor the patient closely because antidepressants can raise the blood level of the antipsychotics and vice versa.[35,66]

Not much is known about how effective the newer antidepressants are in treating psychotic depression, but venlafaxine would not be a good choice, as it can exacerbate psychotic symptoms in vulnerable patients.[67] Tricyclic antidepressants, the most well-studied agents for psychotic depression, usually provide successful results. Nevertheless, they can cause frank psychosis themselves, especially in the elderly, perhaps because of their anticholinergic properties.[68] The SSRIs also play a role in the treatment of psychotic depression, particularly when combined with an antipsychotic agent.[69]

When pharmacotherapy is unsuccessful or contraindicated, electroconvulsive therapy can be prescribed and is frequently successful.[60] Any patient who requires electroconvulsive therapy should be hospitalized and will need referral to a psychiatrist. In fact, many authorities recommend hospitalization for virtually all psychotic depressive episodes, especially when the patient is suicidal.[5,43,44]

Conclusions

Depression is common in a primary care practice, and depressed patients can have complicating features, such as bipolar disorder, suicidal ideation, or psychosis. Bipolar disorder differs from unipolar depression in that bipolar disorder can be inherited and it produces manic or hypomanic episodes. Antidepressants can cause a switch from depression to mania, so this complication should be monitored when prescribing antidepressants for patients with bipolar disorder.

Suicidal ideation is common in depression and should always be asked about when examining a depressed patient. These patients need vigorous treatment at full doses to relieve suicidal urges resulting from the depression. Physicians should be aware of the low lethal dose of tricyclic antidepressants, and only a small supply of any antidepressant should be prescribed at any one time. In this regard the SSRIs are advantageous because they are much safer than the tricyclic antidepressants if a patient overdoses; in addition, the usual therapeutic dose is also the starting dose.

Psychotic depression is a severe form of depression that usually requires hospitalization. Either electroconvulsive therapy or a combination of antidepressant and antipsychotic medication is needed for treatment. Patients are more likely to develop a psychotic depression if they have underlying structural abnormalities of the brain. Severe psychomotor changes often signal a psychotic depression, which is confirmed by delusions or, more rarely, hallucinations. Psychiatric referral is generally recommended for these patients.

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