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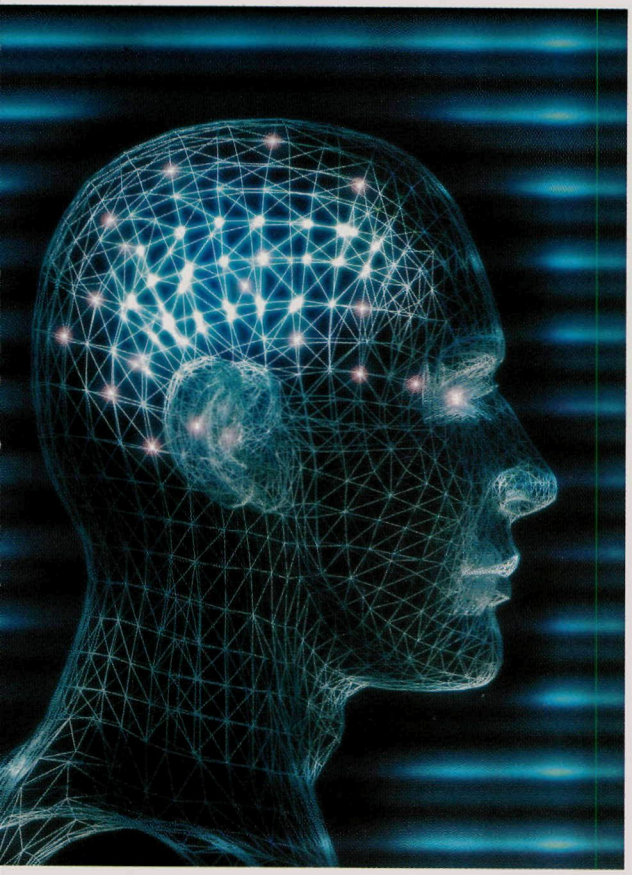

Practical Approaches to Treating Patients with Bipolar Disorder

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Many patients present to a primary care setting with symptoms of a mood disorder. These symptoms may be indicative of an anxiety disorder or a depressive disorder, but they may also represent bipolar disorder, which is more common than many practitioners think. Correctly diagnosing bipolar disorder can be complex, because patients tend to seek treatment when they are experiencing the symptoms of depression or anxiety rather than mania or hypomania. Comorbid disorders such as substance abuse and anxiety disorders may complicate the clinical presentation. Failing to correctly diagnose bipolar disorder can have serious consequences in terms of patients' morbidity and mortality, quality of life, and financial costs.

Primary care nurse practitioners (NPs) frequently see patients who have both medical and psychiatric diagnoses.[1,2] The psychiatric diagnosis may present in a variety of guises and may be hidden under an array of somatic complaints.[3] Mentally healthy individuals experience a vast range of moods throughout their lifetime; this normal fluctuation may fall between euphoria and depression. However, extreme mood swings may alter a person's thoughts, feelings, physical health, behavior, and social functioning, and may represent a more serious cause such as unipolar depression (ie, major depression) or bipolar disorder (alternation between elevated and depressed mood states).[4,5]

Because of the limited time frame available to evaluate each patient, NPs may have difficulty distinguishing between a normal fluctuation of mood and a more extreme fluctuation of mood indicative of a more serious psychiatric disorder.[5] As providers of holistic care, as well as being the sole healthcare providers that many patients see, NPs are responsible for recognizing, diagnosing, and treating mental illnesses, as well as

making appropriate referrals.[1] The diagnosis of bipolar disorder is often under-recognized because patients tend to report depression, anxiety, insomnia, or substance abuse, while ignoring their episodes of mania or hypomania.[3,5]

- **Unipolar depression:** loss of interest or pleasure in all or almost all activities most of the day, nearly every day; changes in appetite and weight; decreased energy, concentration and memory; increased feelings of hopelessness, helplessness, guilt, fatigue, irritability or restlessness;
- **Anxiety:** excessive worry that is difficult to control and is associated with restlessness, fatigue, poor concentration, irritability, muscle tension and sleep disturbance;
- **Mania:** abnormally elevated, expansive, or irritable mood characterized by grandiosity, decreased need for sleep, pressured speech, flight of ideas, distractibility, psychomotor agitation, and excessive involvement in pleasurable activities without regard to the consequences; and
- **Hypomania:** an abnormality of mood resembling mania but of lesser intensity.[6]

If patients are experiencing acute mania or hypomania, which might signal a diagnosis of bipolar disorder, they are more likely to present to an emergency department (ED) rather than to a primary care setting.[5,7]

Historical Overview of Mood Disorders

Reviewing the history of mood disorders provides insight into the persisting stigmata associated with mental illness. Mood disorders were initially described by the ancient Greeks and Romans, who coined the terms *mania* and *melancholia* and identified them as two distinct disorders.[8,9] One treatment recommended for euphoric, agitated, or melancholic patients was bathing in the waters of northern Italian spas. A natural supply of lithium salts was later discovered to be present in these waters.[8]

In 300 BC, Hippocrates described the link between "the four humors"—which he labeled blood, black bile, yellow bile, and phlegm—and physical health.[10] Hippocrates' support of the physical origin of mental disorders was contrary to the popular belief of the time period—that mental illness was caused by magical or supernatural forces.[8]

In the second century AD, Areteus of Cappadocia thought that euphoria and depression might coexist as two attributes of one disorder.[8,10,11] After the decline of the Roman Empire, devil possession was believed to be the cause of mania and depression. Treatments included restraints, euthanasia, exotic potions, bloodletting, and application of electric eels to the skull.[8]

The term *manico-melancolicus* was coined by Theophile Bonet in 1686 to describe the relationship between mania and melancholia.[11] A more modern conceptualization was described by Jean-Pierre Fairet in the 1850s as *folie circulaire,* meaning "circular insanity"; *folie* can also mean "double form," which describes the attacks of both mania and depression that characterize bipolar disorder.[8,12] This early identification encompassed a wide range of affective disorders that included unipolar and bipolar depression.[12] In 1921, Emil Kraepelin published *Manic-Depressive Insanity and Paranoia,* which suggested for the first time that severe psychotic depression could have alternating forms of mania and severe melancholy.[13] Since then, the complicated subtypes of bipolar disorder have been identified and diagnostic criteria established.

Incidence

Each year, 20% to 23% of US adults suffer from depression and 38% from an anxiety disorder.[4,14] The incidence of bipolar I disorder is approximately 1%,[15,16] but if the broader spectrum of bipolar disorders is included, then the incidence may be as high as 8%,[1,15-21] leading the World Health Organization (WHO) to identify bipolar disorder as the sixth leading cause of disability for persons aged 15 to 65.[20,22] Two thirds of patients with bipolar disorder have impairment in both occupational and functional domains, and instability in social and intimate relationships.

Bipolar disorder is equally common in men and women,[2,17-21] although research indicates that women are 3 times more likely than men to experience rapid cycling.[23,24] Further studies have indicated that bipolar II disorder may be more common in women than in men.[10,24] The incidence of bipolar disorder in children and adolescents is more difficult to determine. In the past, this disorder was thought to be rare or nonexistent in children.[19] Findings in one National Institute of Mental Health (NIMH) study suggested that bipolar disorder was as common in young people as it is in adults.[23] A study on 82 children with pediatric bipolar disorder (mean age, 11 years), showed that in 74% of the participants, psychopathologic manifestations such as mood and

sleep disturbances, hyperactivity, aggression, and anxiety were recognized before age 3 years.[19] Ninety percent of the participants had a family history of mood or substance abuse disorders.[19]

Etiology and Pathophysiology

The etiology of bipolar disorder is complex, and seems to be related to the interaction of various genetic and non-genetic factors.[23,24] The genetic link has been suggested by the results of family, twin, and adoption studies.[10,23,24] First-degree relatives of a person with bipolar disorder, as compared with the general population, are approximately 7 times more likely to develop the disorder.[24]

Despite the identification of a genetic link, the understanding of the pathophysiology of bipolar disorder is limited.[20] Several different neurotransmitters have been linked to bipolar disorder; these links have been based on patients' responses to psychoactive agents. For example, patients treated with reserpine incidentally experience depression. Because reserpine depletes catecholamines from nerve tissues, researchers hypothesized that an increase in epinephrine and norepinephrine induces mania, whereas a decrease in these neurotransmitters causes depression. Cocaine, another drug that acts on this neurotransmitter system, exacerbates mania. Levodopa also exacerbates mania, suggesting that dopamine and serotonin are linked to bipolar disorder. Finally, hormonal imbalances and disruptions of the hypothalamic–pituitary–adrenal axis may contribute to the clinical presentation of bipolar disorder.[24]

Non-genetic factors, including psychological stress, thyroid disease, and sleep deprivation, may be closely intertwined with a genetic predisposition to bipolar disorder.[10,23-25] One psychodynamic theory identifies the depressive side of the disorder as a manifestation of losses, and the manic side as a defense against depression.[24]

Definitions and Diagnostic Criteria

The *Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition, Text Revision (DSM-IV-TR)* identifies the criteria used to diagnose bipolar I disorder, bipolar II disorder, cyclothymia, and bipolar disorder, not otherwise specified (NOS) (Table 1).[6] To increase recognition of bipolar disorder, this diagnosis should be considered in all patients who present with symptoms of a mood disorder.[5,10] Specific features provide clues to making an accurate diagnosis. Red flags include a family history of bipolar disorder, an early age of onset (<25 years), frequent episodes, rapid cycling, psychotic features, seasonal patterns, and poor response to antidepressants (eg, treatment-emergent hypomania, lack of response to multiple trials of different antidepressants).[5,7,15,16]

In children and adolescents, NPs need to distinguish bipolar disorder from other behavioral disorders. Red flags for identifying bipolar disorder in children and adolescents include inflated self-esteem or grandiosity, increased goal-directed activity, flight of ideas, decreased need for sleep, excessive involvement in pleasurable activities without concern for adverse consequences, and pronounced sexual energy.[19]

TABLE 1 BIPOLAR SPECTRUM DISORDERS[6]

- **BIPOLAR I DISORDER:** Presence or history of at least one manic episode, with or without a history of major depressive episode(s) that cannot be accounted for by another disorder; the episode must have lasted at least a week (unless functional impairment is so great that hospitalization is required)
- **BIPOLAR II DISORDER:** Presence or history of at least one hypomanic episode and one or more major depressive episode(s) that cannot be accounted for by another disorder
- **CYCLOTHYMIA:** Presence of numerous periods of hypomanic symptoms interspersed with numerous periods of depressive symptoms, but to a lesser degree than those occurring with bipolar I or bipolar II, and occurring almost consistently during a 2-year time period (1 year of symptoms in children and adolescents)
- **BIPOLAR DISORDER, NOT OTHERWISE SPECIFIED:** Residual diagnostic category for bipolar features that do not meet diagnostic criteria for bipolar I, bipolar II, or cyclothymia. This diagnostic category may be used during the period of initial diagnosis if a secondary cause for the symptoms such as substance abuse or a medical condition is being considered.

Adapted from American Psychiatric Association. *Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition, Text Revision.* Washington, DC: American Psychiatric Association; 2000:375-376.

The Mood Disorder Questionnaire (MDQ) is a validated screening tool for bipolar depression (Table 2).[26] This questionnaire can help identify 70% of patients with bipolar disorder while eliminating the diagnosis in 90% of persons without the diagnosis. The MDQ is easily administered by primary care providers or it can be self-administered by patients. It contains 15 questions focusing on behavioral symptoms and on the family and personal history. The test takes about 5 minutes to complete. Some patients may have only 3 or 4 positive answers to the MDQ, which is insufficient to meet criteria for bipolar disorder (7 of 13 positive answers). Nevertheless, in these cases, NPs should be alert for future manifestations of this illness. The MDQ has another important function—it may make patients more aware of symptoms that they may have disregarded in the past.[5]

Distinguishing Bipolar Depression from Unipolar Depression in Adults

Bipolar disorder is a complicated diagnosis because of the lack of a consistent pattern of presentation. Differentiating bipolar depression from unipolar depression is a challenge; misdiagnosis is common. A chart review of 85 patients with bipolar or unipolar depression showed that 56% of the patients were originally misdiagnosed,[27] usually with unipolar depression or an anxiety disorder.[5,17,18,28]

Comorbid psychiatric conditions may obscure the clinical picture, adding to the difficulty of making an accurate diagnosis.[19,23] Sixty-five percent of bipolar patients have a comorbid psychiatric axis I disorder (ie, a major mental disorder such as depression, anxiety, schizophrenia, attention-deficit hyperactivity disorder, post-traumatic stress disorder) and 25% have three or more diagnoses.[23] An NIMH study of patients with bipolar disorder showed that 42% also met criteria for post-traumatic stress disorder.[10] Underlying personality disorders also complicate the picture—many features of bipolar disorder and borderline personality disorder overlap.[29,30] Finally, approximately 60% of patients with bipolar disorder self-medicate with alcohol, marijuana, or other illicit substances, making accurate diagnosis of bipolar disorder even more complicated.[5,7,23]

Many patients with bipolar disorder function adequately in their social life and view their hypomanic periods as productive.[31] Thus, they tend to seek medical care only during the depressed phase of their illness. When patients are depressed, they may be unable to recall episodes of feeling good.[5,19] NPs need to bear in mind that a depressed mood may not be specific to a depressive disorder but may also occur transitionally during a manic episode or pervasively.[32] Therefore, bipolar disorder needs to be included in the differential diagnosis whenever a patient presents with symptoms of depression.

Distinguishing Bipolar Disorder from Behavior Disorders in Children and Adolescents

Identifying bipolar disorder in young persons is complicated by the fact that the diagnostic criteria are based on symptoms found in adults (research on age-appropriate criteria is limited).[33,34] Manifestations of bipolar disorder typically appear during the teenage years or early 20s (median age of onset, 17.5 years).[10,15,16,19,23]

One challenge in recognizing bipolar disorder in children and adolescents is that they may present with disruptive behaviors that can be confused with attention deficit hyperactivity disorder (ADHD), oppositional defiant disorder (ODD), or conduct disorder (CD).[19,23,33,34] Also, certain manifestations of bipolar disorder (eg, excessive talking, distractibility, increased activity level, restlessness, loss of normal social inhibitions) overlap with those of ADHD. Furthermore, the diagnoses of ADHD and bipolar disorder may coexist.[20]

CD, a more severe form of ODD, manifests in severe behavioral problems such as aggression toward people and animals, destruction of property, deceitfulness, theft, or serious violation of rules. Children with bipolar disorder may manifest their irritability in a violent manner as well. Thus, NPs need to distinguish between the two disorders. In children with bipolar disorder, the onset of irritable, impulsive outbursts is rapid, whereas in children with ODD or CD, the onset is slower and progresses from minor infarctions to more severe rule-breaking. Further, children with bipolar disorder tend to have episodic outbursts rather than a continual progression, and they generally express guilt and remorse following an outburst.[34]

When to Refer

In the case of most children and adolescents, evaluation and management are considered outside the scope of primary care practice.[34] Even psychiatrists and other specialists in the field of mental health may take up to 8 years to accurately diagnose bipolar disorder.[35] Because

many patients with bipolar disorder will first present to a primary care provider, NPs will still need to provide a preliminary diagnosis and, possibly, initiate treatment for highly symptomatic patients before making appropriate referral. The remainder of this article provides the information that primary care NPs need to start the process.

Diagnostic and Medical Evaluation

Physical causes, including medical conditions (Table 3) and use of certain pharmacologic agents (Table 4), must be excluded when patients present with symptoms consistent with a mood disorder. In addition, patients with bipolar disorder, as compared with the general population, have a higher

TABLE 2 MOOD DISORDER QUESTIONNAIRE[26]

Please answer each question as best you can. Circle Yes or No.

1. Has there ever been a period of time when you were not your usual self and...

- you felt so good or so hyper that other people thought you were not your normal self or you were so hyper that you got into trouble? Yes No
- you were so irritable that you shouted at people or started fights or arguments? Yes No
- you felt much more self-confident than usual? Yes No
- you got much less sleep than usual and found you didn't really miss it? Yes No
- you were much more talkative or spoke much faster than usual? Yes No
- thoughts raced through your head or you couldn't slow your mind down? Yes No
- you were so easily distracted by things around you that you had trouble concentrating or staying on track? Yes No
- you had much more energy than usual? Yes No
- you were much more active or did many more things than usual? Yes No
- you were much more social or outgoing than usual—for example, you telephoned friends in the middle of the night? Yes No
- you were much more interested in sex than usual? Yes No
- you did things that were unusual for you or that other people might have thought were excessive, foolish, or risky? Yes No
- spending money got you or your family into trouble? Yes No

2. If you circled "Yes" to more than one of the questions above, have several of these episodes ever happened during the same period of time? Yes No

3. How much of a problem did any of these episodes cause you (eg, being unable to work; having family, money, or legal troubles; getting into arguments or fights)?
Please circle one response only. No Problem Minor Problem Moderate Problem Serious Problem

4. Have any of your blood relatives (ie, children, siblings, parents, grandparents, aunts, uncles) had manic-depressive illness or bipolar disorder? Yes No

5. Has a healthcare professional ever told you that you have manic-depressive illness or bipolar disorder? Yes No

Score:

Question 1: 7 out of 13 "Yes" responses; Question 2: 1 positive "Yes" response; Question 3: "Moderate" or "Serious"

Positive Screen: All 3 criteria met in Questions 1, 2, and 3.

lifetime incidence of many medical conditions, necessitating careful history taking and performance of a physical examination before making a diagnosis of bipolar disorder or beginning a medication regimen.

No single diagnostic study is used to make the diagnosis of bipolar disorder. However, several laboratory tests must be ordered before making the diagnosis to rule out an underlying medical cause that may mimic or precipitate the depressive or manic side of bipolar disorder. Another reason for ordering laboratory tests is to ensure that certain body systems are functioning adequately; otherwise, patients may not tolerate medications such as lithium, anticonvulsants, or "atypical" antipsychotics.[24]

A complete blood cell count (CBC) with differential will rule out anemia as a cause of the depression. These blood tests are also important because certain anticonvulsants may depress bone marrow, and lithium may cause a reversible increase in the white blood cell count. A sedimentation rate is measured to exclude an underlying disease process such as systemic lupus erythematosus (SLE), infection, or malignancy.[36] If SLE is suspected, then an antinuclear antibody test is performed. A fasting glucose level is ordered to rule out diabetes mellitus; the atypical antipsychotics have been associated with both weight gain and blood glucose dysregulation. An electrolyte panel is ordered because (1) hyponatremia may manifest as depression, (2) lithium use may cause renal and/or electrolyte problems, and (3) hyponatremia may lead to elevated lithium levels, possibly resulting in lithium toxicity. Serum calcium is measured because hypocalcemia may be associated with mental status changes and because hypercalcemia is associated with hyperparathyroidism, which may cause depression. Serum protein levels are measured in patients who present with depression and loss of appetite/anorexia; low serum protein levels may affect the way certain medications are metabolized. Thyroid function tests are performed to rule out hyperthyroidism (associated with manic symptoms) and hypothyroidism (associated with depressive symptoms).[24]

A toxicology screen is ordered because persons who abuse alcohol or other drugs may present with symptoms of mania or depression, and because many patients with bipolar disorder have a comorbid drug or alcohol addiction that should be uncovered. An HIV test is considered in persons at high risk; AIDS causes changes in mental status, including depression. NPs may also consider ordering tests to check for syphilis, which alters mental status. Renal function tests (serum creatinine, blood urea nitrogen) are performed to rule out renal dysfunction, which may present as depression. A baseline electrocardiogram (ECG) is obtained because many antidepressants (especially the tricyclic antidepressants [TCAs]), the atypical antipsychotics, and lithium can affect the heart and lead to rhythm abnormalities.[9,24]

TABLE 3 MEDICAL CONDITIONS THAT MAY CAUSE CHANGES IN MOOD AND BEHAVIOR

NEUROLOGIC DISORDERS: Seizures, tumors, cerebrovascular accident, subdural hematoma/closed head injury, neurodegenerative diseases, Parkinson's disease, Huntington's disease, Alzheimer's disease, Wilson's disease

ENDOCRINOLOGIC DISORDERS: Thyroid disease, adrenal disease

METABOLIC DISORDERS: Electrolyte imbalance, uremia, thiamine deficiency, vitamin B_{12} deficiency, porphyria, postoperative status

CARDIAC DISORDERS: Coronary artery disease

IMMUNOLOGIC DISORDERS: Systemic lupus erythematosus, fibromyalgia

DEMYELINATING DISEASE: Multiple sclerosis

MALIGNANCY: Pancreatic cancer, calcium-related multiple myeloma

INFECTIOUS DISEASES: Syphilis, encephalitis, HIV infection, hepatitis A or B, infectious mononucleosis, influenza, Lyme disease, herpes encephalitis

PHARMACOLOGIC-RELATED AND OTHER TOXICITIES: Acute intoxication or withdrawal from prescribed, over-the-counter, or illicit drugs; heavy metal poisoning; carbon monoxide poisoning

Pharmacologic Treatment Options

In many cases, treatment for bipolar I disorder is managed by a psychiatrist in an inpatient setting. Nevertheless, many patients present with less overt symptoms in the primary care setting, and some patients may resist seeing a mental healthcare provider. Thus, primary care NPs need to know the types of medications that are available to treat bipolar disorder.

The list includes *mood stabilizers* (eg, lithium), *anticonvulsants,* and *antidepressants,* which include selective serotonin inhibitors (SSRIs), monoamine oxidase inhibitors (MAOIs), and TCAs.[28] Some patients with psychotic features may also require treatment with an antipsychotic agent, including one of the newer second-generation atypical antipsychotics. Table 5 provides an overview of pharmacologic treatment strategies.[28]

Lithium—The first medication used successfully to treat mania, lithium (Eskalith® and others) remains a first-line pharmacologic option, with data clearly supporting its efficacy in reducing suicidal ideation in patients with bipolar disorder.[37] Lithium may take several weeks to achieve a therapeutic effect; severely impaired patients may need an additional mood-stabilizing or antipsychotic agent to treat symptomatology. Side effects may include nausea, diarrhea, tremor, polyuria, and polydipsia, which are managed by reducing the total daily dose or adjusting the dosing schedule. Patients on long-term lithium may develop hypothyroidism and, in rare cases, renal insufficiency. Serum lithium levels must be monitored judiciously to prevent neurotoxicity, which may occur when peak serum levels exceed 2.0 mEq per L.[6] In general, a serum lithium level range of 0.5 to 1.4 mEq per L is recommended for acute treatment and prophylaxis.[10] Because lithium is renally excreted, NPs must exercise caution when prescribing it in combination with nonsteroidal anti-inflammatory drugs, thiazide diuretics, angiotensin-converting enzyme inhibitors or angiotensin II receptor blockers (these agents may slow kidney function, causing increased serum lithium levels).

Antiepileptic Drugs—AEDs have become increasingly popular for patients who need a mood stabilizer. These agents may be used with lithium or as monotherapy in patients who have failed lithium treatment. Valproic acid and its derivatives (eg, divalproex sodium, valproate sodium) are considered first-line agents for patients with acute manic or mixed episodes, and are often used for long-term maintenance.[6] The most common side effects of valproic acid are nausea, vomiting, diarrhea, and sedation. NPs should routinely monitor patients' serum valproate levels, liver function, and CBC because serious adverse events, include hepatotoxicity, pancreatitis, and thrombocytopenia, may occur. Valproic acid must be prescribed

TABLE 4 PHARMACOLOGIC AGENTS THAT MAY INDUCE MANIA/DEPRESSION

MANIA	
Amphetamines	Captopril
Anticholinergics	Cimetidine
Benztropine	Disulfiram
Bupropion	Hydralazine
Caffeine	Isoniazid
Corticosteroids	Levodopa
Cyclosporine	Levothyroxine
Baclofen	Methylphenidate
Bromocriptine	Monoamine oxidase inhibitors

DEPRESSION	
Acyclovir	Estrogens
Alcohol	Fluoroquinolones
Anticonvulsants	Histamine H_2-receptor antagonists
Asparaginase	HMG-CoA reductase inhibitors (statins)
Baclofen	Interferon-alfa
Barbiturates	Isotretinoin
Beta-adrenergic blockers	Mefloquine
Bromocriptine	Methyldopa
Calcium channel blockers	Metoclopramide
Corticosteroids	Metrizamide
Cycloserine	Metronidazole
Dapsone	Opioids
Disopyramide	Progestins
Disulfiram	Sulfonamides

with caution to reproductive-aged women because this agent is teratogenic, can induce menstrual irregularities, and can increase the risk of developing polycystic ovary syndrome.[38] Carbamazepine extended-release (Tegretol®-XR, Carbatrol®) has been approved to treat mania, and lamotrigine has been approved for maintenance therapy.

Antipsychotics—Atypical (second-generation) antipsychotics, including clozapine (Clozaril®), olanzapine (Zyprexa®), risperidone (Risperdal®), quetiapine (Seroquel®), ziprasidone (Geodon®), and aripiprazole (Abilify®), are commonly used to treat psychotic symptoms of bipolar disorder. These agents are preferable to first-generation agents (eg, haloperidol, chlorpromazine) because they are less likely to induce extrapyramidal symptoms (EPS) such as akathisia and tardive dyskinesia.[38] Onset of action is fairly rapid, and treatment response may be seen within the first week of use.

Except for clozapine, all of the atypicals are approved by the Food and Drug Administration (FDA) as monotherapy for mania or for use with mood stabilizers. Olanzapine is FDA approved for maintenance therapy, and, when used with the SSRI fluoxetine (Prozac®), is approved to treat bipolar depression. Quetiapine was recently approved to treat bipolar depression.[39]

When prescribing atypicals, NPs need to monitor patients for EPS, which are managed with anticholinergics, antihistamines, beta blockers, or benzodiazepines. Patients using atypicals must also be monitored for weight gain, diabetes, insulin resistance, and alterations in lipid profiles.[40]

Antidepressants and Anxiolytics—SSRIs, MAOIs, and TCAs are often used to treat acute depressive episodes in patients with bipolar disorder or to manage patients who are lithium refractory.[27] Antidepressants, with the possible exception of bupropion (Wellbutrin®), can trigger mania in patients with bipolar disorder, so their use is controversial.[41] Benzodiazepines such as lorazepam (Ativan®) and clonazepam (Klonopin®) have been used for rapid treatment of agitation, insomnia, and anxiety in patients with manic or hypomanic symptoms until the mood stabilizer they are using reaches a therapeutic effect. Patients with comorbid psychiatric problems should be referred to a psychiatric clinician who has expertise in treating the full spectrum of psychiatric illnesses.

Cognitive-Behavioral Therapy

Medications alone do not help patients with bipolar disorder attain optimal levels of functioning.[42] Recent research has suggested that patients with bipolar disorder have better outcomes (eg, reduced likelihood of relapse, improved adherence to their medication regimen) when they receive psychotherapy such as cognitive-behavioral therapy (CBT) along with medication.[23,43] Patients with bipolar disorder need to learn skills to cope with psychosocial stressors that may trigger a symptomatic episode. CBT can help foster a sense of personal empowerment while reducing the social stigma of having a mental illness.[42] When treating bipolar patients, NPs should refer them to a professional therapist to supplement the plan of care.

Implications for NPs

Misdiagnosing bipolar disorder can have serious consequences because morbidity and mortality (eg, functional impairment, suicide) occur at a higher rate in patients with bipolar disorder than in those with major depression.[1,19,22] In all scopes of practice, bipolar disorder is much less recognized than unipolar depression. Approximately 70% of patients with bipolar disorder have received at least one misdiagnosis (mean, 3.5 misdiagnoses).[15,16,31] Primary care practitioners are not the only group of healthcare professionals with a high rate of misdiagnosis of bipolar disorder; on average, mental healthcare providers take up to 8 years to recognize this illness.[35] This delay in diagnosis may be due to the fact that of the two poles of a bipolar disorder, mania is more dramatic and has been the major area of research, to the exclusion of bipolar depression or mixed states.[12,35]

NPs should follow a systemic treatment plan in managing bipolar disorder. This plan may include prescribing medications and making appropriate referrals to a psychiatric clinician or to the ED for hospitalization in the case of acute mania. Patients who give any indication that they are a danger to themselves or to others, who are gravely disabled or out of control, or who have a concurrent medical condition such as liver failure or a cardiac condition that warrants close monitoring should be hospitalized.[24]

Finally, NPs need to help de-stigmatize all forms of mental illness,[44] which can be done by developing supportive relationships with patients and their families. Patients should be empowered with hope, education, and support. NPs also must individualize the treatment plan to the specific characteristics and patterns of each patient, and should keep in mind each patient's underlying co-morbidities and financial and social situations, which may all affect treatment success.[7]

Conclusion

Because of the high prevalence of bipolar disorder, primary care NPs will likely encounter patients with this illness in their practice. Each patient seen for depression and/or anxiety should be screened for bipolar disorder. Early detection of bipolar illness can help patients reach a stable mood in a shorter period of time. Developing a therapeutic alliance with patients can help ensure adherence to the medication regimen. NPs must use a collaborative approach, referring patients to experts in psychiatric illness, as well as therapists to help teach patients skills to understand and cope with their illness. An individualized treatment plan that

TABLE 5 BIPOLAR DISORDER PHARMACOLOGIC TREATMENT STRATEGIES[28]

MEDICATION (EXAMPLES)	MANIA MONOTHERAPY	BIPOLAR DEPRESSION	MAINTENANCE/ PROPHYLAXIS	CONCERNS
Lithium carbonate (Duralith®, Eskalith®, Lithobid®)	FDA approved. Classic bipolar I symptoms. May have an antisuicide effect. Monitoring blood levels is critical.	Not FDA approved. Recommended by the APA guidelines as first-line therapy.	FDA approved since 1978. Research has indicated Li to be better than placebo in prolonging time to intervention for a manic event.	Monitoring blood levels is critical because of the risk for toxicity and life-threatening SE at lithium blood levels >2.0 mEq/L.
Anticonvulsants				
Divalproex sodium (Depacon®, Depakote®)	FDA approved. Proven effective in treating and preventing mania.	Not FDA approved. No published controlled trials. May be useful in rapid-cycling bipolar disorders or aggression.	Not FDA approved. Research suggests better outcomes than with Li or placebo (eg, better medication adherence, less deterioration (per symptoms of depression and GAF scores).	Monitoring of blood levels needed to determine therapeutic range. Monitor for hepatic toxicity, increased appetite with weight gain.
Carbamazepine ER (Carbatrol®, Epitol®, Tegretol®)	FDA approved. Not as effective as divalproex in a randomized blind study.[29] May be effective in patients who have not responded to Li therapy.[3,9]	Not FDA approved. Two research studies have suggested significant improvement from baseline in patients with acute bipolar depression.[9]	Not FDA approved. Controversial research findings when compared with Li for maintenance trials. Li superior on primary measures, whereas carbamazepine superior in bipolar patients with atypical features.	Inconsistency among dose, serum concentration, response, and SE. Monitor hematologic parameters and liver function tests frequently during first 2 months of therapy.
Lamotrigine (Lamictal®)	Not FDA approved. No research studies support the use of lamotrigine for acute mania.	Not FDA approved. Several research studies indicate that lamotrigine is more effective than placebo in controlling symptoms of bipolar depression. Recommended by APA guidelines as first-line therapy for acute bipolar depression.	FDA approved. Two research studies indicated a prolonged time to recurrence of a depressive episode.	Levels increased by divalproex sodium. Levels decreased by carbamazepine and acetaminophen. Start at a low dosage and titrate slowly to reduce risk of Stevens-Johnson syndrome. Do not administer to persons with any type of rash.

takes into account the individual's unique characteristics and underlying comorbidities will help reduce the financial and social stigmata of this common mental health problem. ■

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TABLE 5 BIPOLAR DISORDER PHARMACOLOGIC TREATMENT STRATEGIES[28] (Continued)

MEDICATION (EXAMPLES)	MANIA MONOTHERAPY	BIPOLAR DEPRESSION	MAINTENANCE/ PROPHYLAXIS	CONCERNS
Atypical Antipsychotics				
Clozapine (Clozaril®)	Not FDA approved. Initial research suggests clozapine to be effective.	Not FDA approved.	Not FDA approved.	Sedation+++, weight gain+++. Of concern: associated incidence of agranulocytosis, may lower oral contraceptive efficacy. Risk of diabetes. QTc prolongation. Risk for EPS and NMS.
Olanzapine (Zyprexa®)	FDA approved alone or with Li or valproate to increase antimanic efficacy.	FDA approved when combined with fluoxetine.	FDA approved. May reduce time to recurrence of mania or depression.	Sedation++, weight gain+++. Risk of diabetes and dyslipidemia. Risk for EPS and NMS.
Risperidone (Risperdal®)	FDA approved for short-term treatment of acute mania or mixed episodes associated with bipolar I.	Not FDA approved as monotherapy. May be used in combination with Li or valproate.	Not FDA approved. May reduce time to recurrence of mania or depression.	Increased prolactin levels, weight gain +++. Increased TG and cholesterol levels. Risk for EPS and NMS.
Quetiapine (Seroquel®)	FDA approved for acute mania in bipolar I disorder. May be used in combination with Li or valproate to increase antimanic efficacy. FDA approved as mania combination therapy.	FDA approved in 2006 for depressive episodes associated with bipolar disorder	Currently under clinical trial investigation.	Somnolence, dizziness, dry mouth, constipation. Risk of weight gain, diabetes, and dyslipidemia. May increase LFT values. Risk for EPS and NMS. Ocular lens changes; monitor for cataracts q 6 months.
Ziprasidone (Geodon®)	FDA approved for acute mania or mixed episodes associated with bipolar I.	FDA approved in 2001 for treatment of schizophrenia and schizoaffective disorder. Not FDA approved for bipolar depression.	Not FDA approved.	Contraindicated in patients with history of QT prolongation, recent MI, CHF. Risk of weight gain, diabetes, and dyslipidemia. Risk for EPS and NMS. Monitor electrolytes. Lower risk of weight gain than other atypicals.
Aripiprazole (Abilify®)	FDA approved for acute mania or mixed episodes associated with bipolar I.	Not FDA approved.	Not FDA approved. One study demonstrated effectiveness for 6 weeks of maintenance therapy after stabilization of acute mania.	Somnolence, headache, anxiety, insomnia, GI upset. Lower risk for obesity, diabetes, and dyslipidemia than other atypicals. Risk for EPS and NMS.

FDA = Food and Drug Administration; APA = American Psychiatric Association; Li = lithium; SE = side effects; GAF = global assessment of functioning; EPS = extrapyramidal symptoms; NMS = neuroleptic malignant syndrome; TG = triglycerides; LFT = liver function test; MI = myocardial infarction; CHF = congestive heart failure; GI = gastrointestinal.

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