Bipolar Disorders: A Review

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Bipolar disorders are common, disabling, recurrent mental health conditions of variable severity. Onset is often in late childhood or early adolescence. Patients with bipolar disorders have higher rates of other mental health disorders and general medical conditions. Early recognition and treatment of bipolar disorders improve outcomes. Treatment of mood episodes depends on the presenting phase of illness: mania, hypomania, mixed state, depression, or maintenance. Psychotherapy and mood stabilizers, such as lithium, anticonvulsants, and antipsychotics, are first-line treatments that should be continued indefinitely because of the risk of relapse. Monotherapy with antidepressants is contraindicated in mixed states, manic episodes, and bipolar I disorder. Maintenance therapy for patients involves screening for suicidal ideation and substance abuse, evaluating adherence to treatment, and recognizing metabolic complications of pharmacotherapy. Active management of body weight reduces complications and improves lipid control. Patients and their support systems should be educated about mood relapse, suicidal ideation, and the effectiveness of early intervention to reduce complications. (*Am Fam Physician.* 2012;85(5):483-493. Copyright © 2012 American Academy of Family Physicians.)

▶ **Patient information:** A handout on bipolar disorders, written by the authors of this article, is provided on page 499.

Bipolar disorders often are first diagnosed in adolescence or early adulthood after several years of symptoms. Symptoms include periods of mania, hypomania, psychosis, or depression interspersed with periods of relative wellness. The clinical course of bipolar disorders varies. Patients rarely experience a single episode, with relapse rates reported at more than 70 percent over five years.[1] Although bipolar disorders are defined by the presence of manic or hypomanic symptoms, most patients are depressed most of the time, which is also a major source of disability.[2]

Bipolar disorders include four subtypes: bipolar I, bipolar II, cyclothymia, and bipolar disorder not otherwise specified *(Table 1)*.[3] Criteria for mood episodes involved in diagnosing bipolar disorders are defined in *Table 2*.[3] Each subtype can be divided using specifiers, such as description of the patient's current or most recent episode. The rapid-cycling specifier can be applied to bipolar I or II disorder if the patient has had at least four mood episodes in the previous 12 months, and the episodes were demarcated by partial or full remission for at least two months or a switch to an episode of opposite polarity (e.g., major depressive episode to manic episode).[3]

Table 1. Definitions of Bipolar Disorders

Disorder	*Definition*
Bipolar I disorder	Manic or mixed episode with or without psychosis and/or major depression
Bipolar II disorder	Hypomanic episode with major depression; no history of manic or mixed episode*
Cyclothymia	Hypomanic and depressive symptoms that do not meet criteria for bipolar II disorder; no major depressive episodes
Bipolar disorder not otherwise specified	Does not meet criteria for major depression, bipolar I disorder, bipolar II disorder, or cyclothymia (e.g., less than one week of manic symptoms without psychosis or hospitalization)

NOTE: *Criteria for mood episodes involved in diagnosing bipolar disorders are defined in Table 2.*

**—Mixed episodes are proposed as a diagnostic feature of bipolar II disorder for the upcoming* Diagnostic and Statistical Manual of Mental Disorders*, 5th ed.*

Information from reference 3.

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Table 2. DSM-IV Criteria for Mood Episodes in the Diagnosis of Bipolar Disorders

Major depressive episode

A. Five (or more) of the following symptoms have been present during the same 2-week period and represent a change from previous functioning; at least one of the symptoms is either (1) depressed mood or (2) loss of interest or pleasure

NOTE: Do not include symptoms that are clearly due to a general medical condition, or mood-incongruent delusions or hallucinations

1. Depressed mood most of the day, nearly every day, as indicated by either subjective report (e.g., feels sad or empty) or observation made by others (e.g., appears tearful). NOTE: In children and adolescents, can be irritable mood
2. Markedly diminished interest or pleasure in all, or almost all, activities most of the day, nearly every day (as indicated by either subjective account or observation made by others)
3. Significant weight loss when not dieting or weight gain (e.g., a change of more than 5% of body weight in a month), or decrease or increase in appetite nearly every day. NOTE: In children, consider failure to make expected weight gains
4. Insomnia or hypersomnia nearly every day
5. Psychomotor agitation or retardation nearly every day (observable by others, not merely subjective feelings of restlessness or being slowed down)
6. Fatigue or loss of energy nearly every day
7. Feelings of worthlessness or excessive or inappropriate guilt (which may be delusional) nearly every day (not merely self-reproach or guilt about being sick)
8. Diminished ability to think or concentrate, or indecisiveness, nearly every day (either by subjective account or as observed by others)
9. Recurrent thoughts of death (not just fear of dying), recurrent suicidal ideation without a specific plan, or a suicide attempt or a specific plan for committing suicide

B. The symptoms do not meet criteria for a Mixed Episode

C. The symptoms cause clinically significant distress or impairment in social, occupational, or other important areas of functioning

D. The symptoms are not due to the direct physiological effects of a substance (e.g., a drug of abuse, a medication) or a general medical condition (e.g., hypothyroidism)

E. The symptoms are not better accounted for by Bereavement, i.e., after the loss of a loved one, the symptoms persist for longer than 2 months or are characterized by marked functional impairment, morbid preoccupation with worthlessness, suicidal ideation, psychotic symptoms, or psychomotor retardation

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 (e.g., 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 (i.e., 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 (e.g., engaging in unrestrained buying sprees, sexual indiscretions, or foolish business investments)

C. The symptoms do not meet criteria for Mixed Episode

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 (e.g., a drug of abuse, a medication, or other treatment) or a general medical condition (e.g., hyperthyroidism)

NOTE: Manic-like episodes that are clearly caused by somatic antidepressant treatment (e.g., medication, electroconvulsive therapy, light therapy) should not count toward a diagnosis of Bipolar I Disorder

Mixed episode

A. The criteria are met both for a Manic Episode and for a Major Depressive Episode (except for duration) nearly every day during at least a 1-week period

B. 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

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

NOTE: Mixed-like episodes that are clearly caused by somatic antidepressant treatment (e.g., medication, electroconvulsive therapy, light therapy) should not count toward a diagnosis of Bipolar I Disorder

continued

Table 2. DSM-IV Criteria for Mood Episodes in the Diagnosis of Bipolar Disorders *(continued)*

Hypomanic episode

A. A distinct period of persistently elevated, expansive, or irritable mood, lasting throughout at least 4 days, that is clearly different from the usual nondepressed mood

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 (e.g., 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 (i.e., 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 (e.g., the person engages in unrestrained buying sprees, sexual indiscretions, or foolish business investments)

C. The episode is associated with an unequivocal change in functioning that is uncharacteristic of the person when not symptomatic

D. The disturbance in mood and the change in functioning are observable by others

E. The episode is not severe enough to cause marked impairment in social or occupational functioning, or to necessitate hospitalization, and there are no psychotic features

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

NOTE: Hypomanic-like episodes that are clearly caused by somatic antidepressant treatment (e.g., medication, electroconvulsive therapy, light therapy) should not count toward a diagnosis of Bipolar II Disorder

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Epidemiology

In 2004, the World Health Organization ranked bipolar disorders collectively as the 12th most common moderately to severely disabling condition in the world for any age group,[4] with a lifetime prevalence of 4 percent in the United States.[5] Bipolar disorders have no predilection for race, sex, or ethnicity. Although they can occur at any age, bipolar disorders are most common in persons younger than 25 years. The mean age at symptom onset is 18 years in bipolar I disorder and 22 years in bipolar II disorder.[5]

Bipolar disorders are common in primary care settings. Among patients presenting with depression or anxiety, 21 to 26 percent will meet criteria for bipolar disorders using a structured interview.[6] Patients with bipolar disorders often have other mental health conditions,[5] most commonly anxiety disorders, impulse control and attention-deficit/hyperactivity disorders, and substance abuse, which are associated with worse outcomes.[7] General medical conditions, including diabetes mellitus, obesity, and cardiovascular disease, are more common in patients with bipolar disorders compared with age-matched cohorts, and cardiovascular risk is higher in those with bipolar disorders than in those with other mental health conditions.[8] Although use of medications to treat bipolar disorders may increase susceptibility to metabolic syndrome, patients with untreated bipolar disorders have significantly higher rates of death from cardiovascular causes.[8] Suicide rates are 20 times higher in patients with bipolar disorders than in the general population.[9] One-third of patients with bipolar disorders attempt suicide, a rate that is among the highest of any psychiatric diagnosis.[10]

Etiology

Children of parents with bipolar disorders have a 4 to 15 percent risk of also being affected, compared with a 0 to 2 percent risk in children of parents without bipolar disorders.[11] Environmental factors are strongly associated with the inheritance pattern.[12] These factors include stressful life events, particularly suicide of a family member; disruptions in the sleep cycle; and family members or caregivers with high expressed emotion, a communication pattern defined as emotionally overinvolved, hostile, and critical.[13] Research indicates that bipolar disorders, schizophrenia, and major depressive disorders share biologic susceptibility and inheritance patterns.[14,15] New data have identified several genes and loci that may be associated with bipolar disorders, including glycogen synthase kinase-3β.[16]

Clinical Presentation

Patients with bipolar disorders often present for treatment with depression or in a mixed state[17] (i.e., depressed mood combined with increased energy, restlessness, and racing thoughts). The diagnosis may be delayed because a series of depressive episodes may occur before a mixed, manic, or hypomanic episode manifests. Physicians need

Table 3. Clues to the Diagnosis of Bipolar Disorders

Symptoms	**Personal history**
Reduced need for sleep for a few days without feeling tired	Multiple divorces
Sleep disruptions (e.g., shift work; childcare; travel; time change; change in season, especially spring and fall) that trigger a manic or hypomanic event	Prior episodes of depression, especially with early onset (age 13 years or younger) or seasonal variability
Atypical depression: hypersomnia, increased appetite, psychosis, pathologic guilt, labile mood	No response to three or more antidepressant trials
Racing thoughts that prevent sleep initiation	Legal or financial problems
Irritability, impulsivity, irrationality	Attempted suicide
Mood swings (irregular changes from low to high) or periods of intense goal orientation	Drug or alcohol abuse
Family history	Recurrent job loss
Relative with a bipolar disorder	Intolerance of an antidepressant, steroid, or other medication, especially if it caused agitation or mania
Multiple relatives with any of the following: depression, obsessive-compulsive disorder, attention-deficit/hyperactivity disorder, anxiety, panic disorder	Prior episodes of mania or hypomania
Family history of multiple instances of suicide, incarceration, drug or alcohol abuse	

Information from reference 18.

to ask all patients with depression if they have had symptoms of mania or hypomania (e.g., changes in energy, racing thoughts, decreased need for sleep, or a mood that was distinctly better than usual for a brief period in the past). Historical clues that raise suspicion for bipolar disorders are listed in *Table 3*.[18] Mixed states are of significant concern because heightened energy increases the risk of suicide.[19]

Evaluation

Screening for depressive disorders is recommended for patients 12 to 18 years of age in practice settings with systems in place to support accurate diagnosis, psychotherapy, and follow-up using the age-appropriate Patient Health Questionnaire (available at http://www.depression-primarycare.org/clinicians/) or the Beck Depression Inventory–Primary Care Version.[20] With a high negative predictive value, office-based tools, including the Bipolar Spectrum Diagnostic Scale, the My Mood Monitor (M-3) checklist, and the Mood Disorder Questionnaire (available at http://www.dbsalliance.org/pdfs/MDQ.pdf), can be useful in ruling out bipolar disorders, but they are not sufficient to confirm a diagnosis.[21-23]

The medical evaluation of patients with a suspected bipolar disorder is based on ruling out other causes of the patient's symptoms *(Table 4*[24]*)* and can assist in selecting a medication. Secondary mania should be more strongly considered in patients presenting with a first episode in prepuberty or after 40 years of age.[25] Appropriate evaluation for diabetes and lipid abnormalities, which are associated with the disorders and their treatment, is also needed. *Table 5* includes tests that can be considered in the evaluation of patients with a suspected bipolar disorder.[25]

Table 4. Selected Causes of Secondary Mania

Drug abuse
Alcohol, amphetamines, cocaine, hallucinogens, opiates
Medications
Cardiovascular: captopril, hydralazine
Endocrine: bromocriptine (Parlodel), corticosteroids
Neurologic agents: levodopa
Psychiatric: antidepressants, disulfiram (Antabuse), methylphenidate (Ritalin), monoamine oxidase inhibitors
Other agents: baclofen (Lioresal), cimetidine (Tagamet), isoniazid
Diseases
Collagen vascular disease: systemic lupus erythematosus
Endocrine disease: Cushing disease, hyper- or hypothyroidism
Infectious disease: herpes encephalitis, human immunodeficiency virus encephalitis, influenza, neurosyphilis
Neurologic disease: complex partial seizures, Huntington chorea, migraine headache, multiple sclerosis, neoplasm, stroke, traumatic brain injury, Wilson disease
Vitamin deficiency: B_{12}, folate, niacin, thiamine

Adapted with permission from Family Practice Notebook. Mania secondary causes. http://www.fpnotebook.com/Psych/Bipolar/MnScndryCs.htm. Accessed September 14, 2011.

Table 5. Medical Tests to Consider in the Evaluation of Patients with a Suspected Bipolar Disorder

Test	*Rationale*
Basic metabolic panel, more detailed evaluation of renal function (in patients with a history of renal disease)	Establishes baseline sodium level and renal function in patients taking antipsychotics, lithium, anticonvulsants, and antidepressants
Complete blood count	Rules out pernicious anemia, establishes baseline measurements in patients taking anticonvulsants
Complete physical examination, including neurologic evaluation	May help rule out systemic illness; establishes baseline measurements of body mass index, blood pressure, and waist circumference, which are monitored in maintenance treatment of bipolar disorders; routine maintenance examination includes monitoring for medication adverse effects, including extrapyramidal effects
Electrocardiography (in patients older than 40 years, in others if indicated)	Establishes baseline measurements in patients taking lithium, antipsychotics, or medications that can prolong the QTc interval (nonpsychiatric medications, such as proton pump inhibitors, carbamazepine [Tegretol], and prochlorperazine)
Fasting glucose level, lipid profile	Rules out diabetes mellitus, hyperlipidemia, and Cushing syndrome and establishes baseline measurements in patients taking any medication that can cause weight gain or hyperglycemia
Liver function tests, prothrombin time and partial thromboplastin time (if electroconvulsive therapy is planned)	May help rule out hepatitis, establishes baseline measurements in patients taking anticonvulsants and antipsychotics
Pregnancy test (if relevant)	Avoids use of teratogenic medications in pregnancy
Prolactin level	Establishes baseline measurements in patients taking antipsychotics, which increase prolactin level
Thyroid-stimulating hormone level	Rules out primary or secondary thyroid disorders, establishes baseline measurements in patients taking lithium
Urinalysis	Helps rule out infection in older patients
Urine toxicology screen	Rules out mood and thought disorders secondary to substance abuse
Additional tests in patient with new-onset psychosis Electroencephalography Magnetic resonance imaging (preferred) or computed tomography If indicated based on clinical suspicion: urine toxicology and studies for heavy metals, urine porphyrins, hepatitis C, and syphilis	Rules out occult seizure disorder, intracranial mass, other causes of secondary psychosis

Information from reference 25.

Treatment

Early diagnosis and treatment of acute mood episodes improve prognosis by reducing the risk of relapse and doubling the rate of response to medications.[26] Medication selection *(Table 6*[6,7,27-30]*)* depends on the presenting phase of illness and its severity. Treatment should continue indefinitely because of the risk of relapse, which occurs in one-third of patients in the first year after presentation and in more than 70 percent of patients within five years.[1] Comanagement with a psychiatrist is often required because of relapse, treatment resistance, comorbid psychiatric conditions, and the risk of patients harming themselves or others. Women of childbearing age should be educated about the teratogenic effects of most mood stabilizers and the importance of using reliable contraception while taking these medications.

Table 6. Drug Therapy for Patients with Bipolar Disorders

Medication	Indication: Acute mania	Indication: Maintenance	Indication: Bipolar depression	Comments
Antipsychotics, atypical				Antipsychotic medication plus lithium or an anticonvulsant is superior to monotherapy for acute mania
Aripiprazole (Abilify)	Yes	No	No	Olanzapine and aripiprazole are effective in preventing manic relapse[7,27]
Olanzapine (Zyprexa)	Yes	Yes	Yes (plus SSRI)	Quetiapine plus lithium or valproate is superior to monotherapy for maintenance treatment
Quetiapine (Seroquel)	Yes	Yes	Yes	
Risperidone (Risperdal)	Yes	Yes	No	
Ziprasidone (Geodon)	Yes	No	No	
Antipsychotics, typical Haloperidol lactate (Haldol)	Yes	No	No	No difference in response rates among haloperidol, risperidone, olanzapine, carbamazepine, and valproate for acute mania
Benzodiazepines Lorazepam (Ativan)	Yes	No	No	Used as combination therapy in patients with acute mania to reduce agitation[6]
Carbamazepine (Tegretol)	Yes	Yes	Yes	Evidence for carbamazepine is not as strong as that for lithium and valproate
Divalproex (Depakote), valproic acid (Depakene)	Yes	Yes	Yes	Valproate appears to be more effective than lithium for mixed states[28]
Lamotrigine (Lamictal)	No	Yes	Yes	Acceptable agent in pregnancy; associated with weight loss in obese patients with bipolar I disorder[29]
Lithium	Yes	Yes	Yes	Lithium lowers suicide risk compared with valproate or carbamazepine Lithium appears to be protective against dementia[30] Adding an SSRI or bupropion (Wellbutrin) does not improve depressive symptoms

SSRI = selective serotonin reuptake inhibitor.

Information from references 6, 7, and 27 through 30.

Monotherapy with antidepressants is contraindicated in patients with mixed states, manic episodes, or bipolar I disorder.

Electroconvulsive therapy can be effective for mania and psychotic depression.[27] Behavioral interventions (e.g., cognitive behavior therapy, caregiver support, psychoeducation regarding the early warning signs of mood relapse) are considered first-line adjuncts to pharmacotherapy to improve social function and reduce the need for medications, number of hospitalizations, and relapse rates.[7,31-33] Early warning signs of a mood relapse include sleep disturbance, agitation, increased goal orientation, and a disruption in usual routine. The risk of suicide is lowered with increased satisfaction with care, lithium therapy, and treatment of alcohol and tobacco abuse.[7,9,34]

ACUTE MANIA

Patients with acute mania need to be hospitalized because they could harm themselves or others. The goal of initial treatment includes adequate sleep and reduction of psychotic symptoms. High-quality evidence supports the use of the mood stabilizers lithium and valproate and of antipsychotics.[7,28,35-37] Lithium is the treatment of choice for classic euphoric mania.[38] It is often given in conjunction with an antipsychotic and a benzodiazepine in the acute phase,[6] because lithium takes a number of days to reach steady state. Combination therapy with lithium or valproate plus an antipsychotic is superior to either agent alone in the resolution of acute mania.[38]

Patients with acute hypomania should be assessed for decision-making capacity and the ability to comply with treatment. An ensuing major depressive episode

is a major source of morbidity in patients with hypomania.

MIXED STATES

Lithium does not benefit patients in mixed states or those who have rapid cycling. Valproate is often used because it can be titrated quickly and has been shown to be effective in mixed states.[27] Although other anticonvulsants are used, there is no evidence to support them.

ACUTE DEPRESSION

Patients with acute depression should be assessed for suicidal or homicidal ideation and the need for inpatient treatment. Recommendations for drug therapy are partly based on the time it takes to titrate the medications. Several agents are effective for acute depression, including lithium.[27] Lamotrigine (Lamictal) is effective, but a minimum of six weeks of titration is needed to mitigate the risk of Stevens-Johnson syndrome. Patients are highly responsive to quetiapine (Seroquel) after one week of use, but the medication is associated with weight gain and extrapyramidal effects.[39]

There is no evidence to support combination therapy or the addition of an antidepressant in the acute phase of depression.[40] In a study of patients with bipolar II disorder, adding paroxetine (Paxil) or bupropion (Wellbutrin) was no more effective than using lithium or valproate alone.[7] If a therapeutic dose of a mood stabilizer does not resolve symptoms and the patient is not in a mixed state, an antidepressant can be added. Patients may also benefit from switching mood stabilizers or adding an antipsychotic if antidepressants are contraindicated.[27] Patients who are resistant to treatment should receive a selective serotonin reuptake inhibitor or bupropion for treatment augmentation when indicated, because either therapy is less likely to induce mania compared with tricyclic antidepressants or medications with dual properties, such as venlafaxine (Effexor).[41] When treating sleep disturbance in patients with depression, physicians should avoid prescribing trazodone because it can induce mania.[42]

MAINTENANCE THERAPY

High-quality evidence supports the use of lithium, lamotrigine, valproate, quetiapine, and olanzapine (Zyprexa) for maintenance therapy in patients with bipolar disorders,[27,43,44] although each has specific advantages and disadvantages *(Table 6*[6,7,27-30]*)*. Quetiapine combined with lithium or valproate is more effective than lithium or valproate alone.[27]

In addition to standard prescription medications, omega-3 fatty acids have a low risk of adverse effects and can help reduce depressive symptoms in patients with bipolar disorders.[45] A randomized controlled study of patients taking olanzapine showed that active management of body weight and a moderate exercise program improved weight loss and lipid profiles over baseline characteristics compared with control groups.[46]

MONITORING

In the maintenance phase, patients with bipolar disorders should receive regular clinical examinations that focus on depressive, manic, and sleep symptoms; suicide risk; comorbid conditions and general medical health; and substance abuse. Patients taking antipsychotic medications are at high risk of metabolic complications and adverse effects. Extrapyramidal effects often manifest early and can include akathisia (i.e., subjective sense of motor restlessness); parkinsonism (i.e., cogwheel rigidity of tendons, masked facies, or muscle stiffness or rigidity); and other movement disorders, such as dystonias and dyskinesias. Tardive dyskinesia is a potentially irreversible movement disorder that can occur within months of initiating antipsychotic therapy in older persons, who are also at risk of stroke and other cardiovascular events, and in patients with neurologic vulnerability (e.g., those with human immunodeficiency virus infection or other central nervous system diseases). Patients taking antipsychotics should be evaluated using the Abnormal Involuntary Movement Scale (http://www.cqaimh.org/pdf/tool_aims.pdf) at each follow-up visit.

Dosage reduction should be considered regularly in patients taking antipsychotic medications. Lower dosages may be required in children or older patients, patients with chronic disease, and patients who are underweight. Higher dosages are required for patients with severe psychosis.[47] *Table 7* summarizes dosing and monitoring recommendations for pharmacotherapy, and specific considerations for individual agents.[6,48-54]

Family and Psychosocial Issues

Psychosocial stress is known to trigger manic and depressive symptoms. Although there are limited and heterogeneous data to support family interventions for bipolar disorders,[55] patients who have social support in recognizing early warning signs of recurrence appear to have less risk of recurrence and hospitalization and have better functioning.[33] Patients who receive intensive psychotherapy[7] or group therapy[31] have fewer relapses and longer periods of relative wellness compared with patients who receive brief therapy. Patients with frequent episodes of mania may benefit from strategies that emphasize medication adherence, whereas those

Table 7. Dosing and Monitoring of Medications for Bipolar Disorders

Medication	*Dosing information*	*Common adverse effects*
Antipsychotics, atypical Aripiprazole (Abilify) Olanzapine (Zyprexa) Quetiapine (Seroquel) Risperidone (Risperdal) Ziprasidone (Geodon)	Varies	Somnolence, dry mouth, orthostatic hypotension, extrapyramidal effects, akathisia, tardive dyskinesia, weight gain, hyperglycemia, neuroleptic malignant syndrome, hyperprolactinemia, sexual dysfunction
Antipsychotics, typical Haloperidol lactate (Haldol)	2 to 5 mg intramuscularly for acute episode; may repeat every hour as needed until symptoms are controlled; switch to oral form as soon as feasible Initial dosage is based on patient's age and severity of symptoms; dosage rarely should exceed 100 mg in 24 hours No recommendation for use after acute episode	Insomnia, restlessness, anxiety, sedation, headache, seizures, weight gain, psychosis, hypotension, tardive dyskinesia, extrapyramidal effects, depression, QT prolongation, neuroleptic malignant syndrome, pneumonia, blood dyscrasia, hyperprolactinemia
Benzodiazepines Lorazepam (Ativan)	0.5 to 2 mg orally or intramuscularly, up to 4 mg per day Reduce dose by 50 percent in patients who are older and debilitated, patients taking valproate, and patients with hepatic or renal disease	Sedation, nausea, blood dyscrasia, extrapyramidal effects, agitation, anterograde amnesia, cognitive impairment, respiratory depression, hyponatremia, syndrome of inappropriate antidiuretic hormone
Carbamazepine (Tegretol)	200 to 1,600 mg orally per day Begin with 200 mg twice per day, adjusting every day by 200 mg as tolerated Titrate to serum level of 4 to 12 mcg per mL	Headache; fatigue; nystagmus; ataxia; rash, including Stevens-Johnson syndrome and toxic epidermal necrolysis*; leukopenia, hyponatremia
Divalproex (Depakote), valproic acid (Depakene)	Target dosage: 1,000 to 3,000 mg orally per day 15 to 20 mg per kg load in patients with acute mania; may also start with 500 to 750 mg per day in divided doses and adjust every two to three days as tolerated Titrate to serum level of 50 to 125 mcg per mL	Tremor, sedation, weight gain, nausea, diarrhea, hair loss, leukopenia, thrombocytopenia, elevated liver transaminase levels, hepatic failure,* pancreatitis,* polycystic ovary syndrome
Lamotrigine (Lamictal)	200 mg orally per day Begin with 25 mg per day, and titrate over six weeks; titration and dosage adjustments differ for those taking valproic acid, carbamazepine, phenytoin (Dilantin), phenobarbital, primidone (Mysoline), rifampin, and oral contraceptives	Dizziness; tremor; somnolence; headache; dry mouth; nausea; rash, including Stevens-Johnson syndrome and toxic epidermal necrolysis*; leukopenia; thrombocytopenia; pancytopenia; aseptic meningitis
Lithium	900 to 1,800 mg orally per day Begin with up to 300 mg twice per day, and adjust dosage every two or three days as tolerated; titrate to serum level of 0.6 to 1.5 mEq per L	Thirst, polyuria, cognitive effects, sedation, tremor, weight gain, diarrhea, nausea, hypothyroidism, diabetes insipidus

CBC = complete blood count.

**—U.S. Food and Drug Administration boxed warning.*

†—*Thyroid-stimulating hormone, total thyroxine, thyroxine uptake.*

Information from references 6, and 48 through 54.

Monitoring recommendations	*Comments*
Lipid profile, fasting blood glucose level, waist circumference, body weight, and CBC in patients with prior clinically significant leukopenia; measure at baseline, monthly in the first three months of therapy, then every three months thereafter	Quetiapine, risperidone, and ziprasidone increase the risk of extrapyramidal effects Aripiprazole is the only atypical antipsychotic not associated with dyslipidemia, but it is associated with akathisia Caution should be used when decreasing dosages because rebound anxiety and psychosis are possible Increased risk of death in older patients with dementia*
CBC (in patients with prior clinically significant leukopenia) at baseline and monthly in the first three months of therapy Prolactin level as clinically indicated Monitor for extrapyramidal effects, tardive dyskinesia, and neuroleptic malignant syndrome	Increased risk of death in older patients with dementia* Torsades de pointes possible, particularly with higher than recommended dosages
Periodic CBC and liver function testing for patients on long-term therapy	Contraindicated in patients with myasthenia gravis or acute narrow-angle glaucoma Avoid in patients with history of substance abuse Continuous long-term use not recommended Paradoxical reactions are more likely in children and older persons; risk of seizure after discontinuation is greater in patients with preexisting seizure disorder and in those taking antidepressants
Serum carbamazepine levels every one to two weeks initially, then every three to six months or before and after dosage changes CBC and liver function testing monthly for the first two months, then every three to 12 months thereafter Screening for *HLA-B1502* in patients with Asian ancestry; patients with positive screening results should avoid carbamazepine because of the risk of Stevens-Johnson syndrome and toxic epidermal necrolysis	Slower titration mitigates adverse effects Hyponatremia occurs in up to 40 percent of patients
Serum valproate levels every one to two weeks initially, then every three to six months or before and after dosage changes CBC and liver function testing monthly for the first two months, then every three to 12 months thereafter	Polycystic ovary syndrome is common in women who start treatment before 20 years of age Teratogenic*
CBC and liver function testing monthly for the first two months, then every three to 12 months thereafter	The incidence of skin rash is reduced with slow titration and by not exceeding the recommended dosage Incidence of serious rash in adults is 0.08 percent with monotherapy
Serum lithium levels every one to two weeks initially, then every three to six months thereafter or before and after dosage changes Thyroid function testing† and renal indices every two or three months in the first six months of therapy, then every six to 12 months thereafter	Toxicity is dose dependent; overdose can be fatal* Incidence of hypothyroidism is higher in women and increases with age High rates of withdrawal compared with valproate and lamotrigine in maintenance therapy

SORT: KEY RECOMMENDATIONS FOR PRACTICE

Clinical recommendation	*Evidence rating*	*References*	*Comments*
Patients 12 to 18 years of age should be screened for depressive disorders in practice settings with systems in place to support accurate diagnosis, psychotherapy, and follow-up.	B	20	Systematic review of randomized and controlled clinical trials regarding treatment generalized to screening
Lithium, valproate, and some antipsychotics are effective treatments for acute mania in bipolar disorders.	A	7, 27	Meta-analyses of randomized studies
Lithium, valproate, lamotrigine (Lamictal), and some antipsychotics are effective treatments for acute depression in bipolar disorders.	A	27, 40	Meta-analysis and systematic review of randomized studies
Lithium, valproate, lamotrigine, and some atypical antipsychotics are effective for maintenance therapy of bipolar disorders.	A	27, 43, 44	Meta-analysis and systematic reviews of randomized studies
Social support in recognizing early warning signs of mood relapse improves outcomes in patients with bipolar disorders.	A	33	Systematic review of randomized studies

A = consistent, good-quality patient-oriented evidence; B = inconsistent or limited-quality patient-oriented evidence; C = consensus, disease-oriented evidence, usual practice, expert opinion, or case series. For information about the SORT evidence rating system, go to http://www.aafp.org/afpsort.xml.

with more depressive symptoms benefit from treatments focused on coping strategies and cognitive behavior therapy.[56] Patients, families, and caregivers should establish a plan for addressing suicidal and homicidal ideation quickly if they become apparent.

Data Sources: We searched the Cochrane Database of Systematic Reviews, DynaMed, Essential Evidence Plus, the U.S. Preventive Services Task Force, the Agency for Healthcare Research and Quality, and Clinical Evidence. A PubMed search was completed using the search subject bipolar disorder. Search dates: June 20, 2010, and May 23, 2011.

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