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Bipolar Disorder

WHAT IS BIPOLAR DISORDER?

Bipolar disorder, or manic-depressive illness, is characterized by moods that swing between two opposite poles:

- Periods of mania (with exaggerated euphoria, irritability, or both). To qualify for a diagnosis of bipolar disorder, only one episode of mood elevation needs to be reported.
- Episodes of depression.

Although chemical imbalances in the brain are a key component of bipolar disorder, it is a complex condition that involves genetic, environmental and other factors.

Bipolar Disorder Categories

Bipolar disorder is classified as bipolar disorder I, bipolar disorder II, or cyclothymic disorder according to the pattern and severity of the symptoms. These conditions are most likely part of a single spectrum of the disease; patients with one type may develop another. Nevertheless, they are distinct enough to merit separate classifications, and some experts believe these conditions are actually separate disorders with different biologic factors that account for their differences.

Bipolar Disorder I. Bipolar disorder I is characterized by at least one manic episode, with or without major depression. In 60% to 70% of cases, manic episodes precede or follow depressive episodes in a regular pattern. Episodes are more acute and severe than in the other two categories. Without treatment, patients average four episodes of dysregulated mood each year. With mania, either euphoria or irritability may mark the phase. In addition, there are significant negative effects (such as sexual recklessness, excessive and impulsive shopping, and sudden traveling) on a patient's social life, performance at work, or both. Untreated mania lasts at least a week and it can last for months. Typically, depressive episodes tend to last six to 12 months, if left untreated.

Bipolar Disorder II and Hypomania. Bipolar disorder II is characterized by at least one episode of *hypomania* and at least one episode of major depression. With hypomania the symptoms of mania (typically euphoria) appear in milder forms and are of shorter duration. Patients do not experience manic or mixed episodes, and most return to fully functional levels between episodes. However, bipolar II patients have a more chronic course, significantly more depressive episodes, and shorter periods of being well between episodes than patients with type I have. It is highly associated with the risk for suicide.

Cyclothymic Disorder. While cyclothymic disorder is not as severe as either bipolar disorder II or I, the condition is more chronic. Hypomanic symptoms tend toward irritability as compared to the more euphoric symptoms of bipolar II. (One report, in fact, referred to these patients as having "darker" natures while bipolar II patients were "sunnier.") The disorder lasts at least two years, with single episodes persisting for more than two months. Cyclothymic disorder may be a precursor to full-blown bipolar disorder in some people or it may continue as a low-grade chronic condition.

Course of the Illness

Bipolar disorder can be severe and long-term, or it can be mild with infrequent episodes. The usual pattern of bipolar disorder is one of increasing intensity and duration of symptoms that progresses slowly over many years. (Patients with the disease, however, may experience symptoms in very different ways.) A typical bipolar disorder patient averages eight to 10 manic or depressive episodes over a lifetime. However, some people experience more and some fewer episodes.

Typical Bipolar Cycles. In most cases of bipolar disorder, the depressive phases far outnumber manic phases, and the cycles of mania and depression are neither regular nor predictable. Many patients, in fact, experience mixed mania, or a mixed state, in which both mania and depression coexist.

Rapid Cycling. About 15% of patients with the disorder have a temporary, complicated phase known as *rapid cycling*. With this phase the manic and depressive episodes alternate at least four times a year and, in severe cases, can even progress to several cycles a day. Rapid cycling tends to occur more often in women and in those with bipolar II. Typically, rapid cycling starts in the depressive phase, and, in fact, frequent and severe episodes of depression may be the hallmark of this event. This phase is difficult to treat, particularly since antidepressants can trigger the switch to mania and set up a cyclical pattern.

Symptoms of Bipolar Disorder

Symptoms of the Depression Phase

The symptoms of depression experienced in bipolar disorder are almost identical to those of major depression, the primary form of *unipolar* depressive disorder. They include the following:

- Sad mood.
- Fatigue or loss of energy.
- Sleep problems (insomnia, excessive sleeping, or shallow sleep with frequent awakenings).
- Appetite changes (either an increase or decrease).
- Diminished ability to concentrate or to make decisions.
- Agitation or markedly sedentary behavior.
- Feelings of guilt, pessimism, helplessness, or low self-esteem.
- Loss of interest or pleasure in life.
- Thoughts of, or attempts at, suicide.

Distinguishing Between Unipolar and Bipolar Depression. It is often difficult to differentiate between unipolar and bipolar depression, particularly in bipolar II patients. They may differ in the following ways:

- Bipolar depression typically lasts two to three months—not as long as in major depression (although left untreated some bipolar disorder episodes can last six to 12 months or longer).
- People with unipolar depression can still experience a variety of other moods, but none meet the criteria for a manic state.
- Depressive symptoms in those with bipolar disorder also tend to be atypical. For example, some patients experience increased sleep, gain weight, and feel a heaviness and slowness in their bodies. Other depressed bipolar patients experience impaired sleep, but unlike patients with unipolar depression, they do not feel sleepy the next day.
- Bipolar depressive episodes tend to develop more gradually than do those caused by major depression.

[For more information on unipolar depression, see, Depression.]

Symptoms of the Acute Manic Phase

The acute pure manic phase is always characterized by mood elevation, presented in the following ways:

- exaggerated euphoria (a feeling of great happiness or well being),
- irritability,

- or both.

The episode lasts for at least few days but, in some cases, the episode may last weeks or even months and may be severe enough to require hospitalization.

Other symptoms must also be present to make a diagnosis. Some mental health professionals use the mnemonic device DIGFAST to identify them. In general, for a diagnosis of mania, a patient must have experienced either euphoria with three DIGFAST symptoms or irritability with four of these symptoms:

- D. Distractibility. This is the most common symptom and it is usually characterized by the inability to pay attention to any activity for very long.
- I. Insomnia in mania typically means having high energy and requiring less sleep. (This differs from insomnia in depression, in which the patient has low energy plus an inability to sleep.)
- G. Grandiosity. Patients with this symptom have an inflated sense of themselves, which, in severe cases, can be delusional. Close to 60% of all manic patients experience feelings of omnipotence. Sometimes they feel that they are godlike or have celebrity status.
- F. Flight of ideas. Thoughts literally race.
- A. Activity. An increase in intensity in goal-directed activities occurs, which is related to social behavior, sexual activity, work or school.
- S. Speech. Excessive talking.
- T. Thoughtlessness. Excessive involvement in high-risk activities is present (e.g., unrestrained shopping, promiscuity). Mood disturbance may be severe enough to damage one's job or social functioning or one's relationships with others, or which requires hospitalization to prevent harm to others or to the self.

Some bipolar I patients may experience psychotic symptoms, including thought disorders, hallucinations, and catatonia (a state in which the patient goes into a stupor for long periods, which may give way to short periods of extreme excitement).

Hypomania. With hypomania the symptoms of mania are milder and of shorter duration (but they last at least four days). They do not affect social or work life as dramatically.

Symptoms of Mixed States

Mixed Mania State. Mixed mania (also called mixed episodes) are manic episodes that also have a depressive component. In such a state, mania is present to a significant degree, but depression is present most of the day and nearly every day. Such mixed symptoms occur for at least a week.

Depressive Mixed State. Of interest is a 2002 study describing a mixed bipolar state, tentatively termed depressive mixed state. It was characterized by major depression as the primary emotional state with atypical manic features (e.g., irritability, distractibility, and racing thoughts). Such patients may receive an inaccurate diagnosis of unipolar depression.

WHO GETS BIPOLAR DISORDER?

Between one and two million Americans are thought to suffer from bipolar disorder. Estimates of the lifetime risk for the disorder run between 1.0% and 1.5%. There is some indication that the incidence of bipolar disorder may be increasing, but more research is needed to confirm this.

Gender

Bipolar disorder affects both sexes equally, but there is a higher incidence of rapid cycling, mixed states, and cyclothymia in women. On the other hand, early-onset bipolar disorder tends to occur more frequently in men and it is associated with a more severe condition.

Age

Bipolar disorder is the most common psychotic disorder, and experts believe that it occurs in 1% of people among all age groups.

Early-Onset Bipolar Disorder. In one survey, 59% of bipolar disorder patients had their first symptoms when they were children or adolescents. Typically, there was a very long delay until the condition was diagnosed and treated. Bipolar symptoms in young people closely mimic those in adulthood, but may have slight differences:

- The initial episodes are more likely to be depressive. In fact, a 2001 study reported that 33% of children who experienced major depression developed bipolar I by age 21 and 15% of them had bipolar II disorder.
- Manic phases usually begin in adolescence or young adulthood, with an average age of onset being 18 years. Mood often involves irritability, but in general symptoms, resemble those seen in adults (euphoria and grandiosity, flight of ideas, racing thoughts, and a decreased need for sleep).

Early-onset bipolar disease is also associated with the following characteristics:

- A family history of bipolar disorder. Children with bipolar disorder who have one or more parents with the same disorder often have a more severe form than does the affected parent.
- A higher incidence of comorbidities (accompanying conditions that include panic disorder, conduct disorder, substance abuse, suicidal behavior, and psychotic symptoms during bipolar episodes). Young patients are at higher risk for these complications regardless of the presence or absence of supportive parents.
- The condition is often more severe in children than in adult patients, with a higher risk for mixed mania (simultaneous depression and mania), multiple and frequent cycles, and a long duration of illness without well periods.

Of note, symptoms of bipolar disorder in children are often confused with attention-deficit hyperactivity disorder (ADHD). Furthermore, the two conditions can coincide. In one study, 65% of adolescents with bipolar disorder met criteria for ADHD. Yet another study indicated that close to 25% of children diagnosed with ADHD either already had bipolar disorder or go on to develop it. The risk for both diagnoses is highest in white males. Symptoms are also more severe in people with both conditions.

Adult-Onset Bipolar Disorder. Bipolar disorder can also appear for the first time in people over the age of forty. In fact, age 40 is another peak of onset for women.

Onset Late in Life. Bipolar disorder that occurs late in life often either follows many years of repeated episodes of unipolar depression or it accompanies medical and neurological problems (particularly cerebrovascular disease, such as stroke). It is less likely to be associated with a family history of the disorder than earlier-onset bipolar disorder.

Accompanying Neurologic or Emotional Disorders

Patients with bipolar disorder, especially type II or cyclothymic disorder, have frequent episodes of major depression. Anxiety disorders also commonly coexist in these patients. For example, the occurrence of panic disorder in bipolar patients is 26 times that of the general population. Bipolar patients, particularly those with type II, are also subject to phobias. In one study, the presence of anxiety disorders was also associated with longer and more severe bipolar depressive episodes and with a higher risk for suicide.

Bipolar disorder in children can also be mistaken for attention-deficit hyperactivity disorder (ADHD). In some cases, ADHD in children or adolescents may be a marker for an emerging bipolar disorder.

Some experts believe that many of these disorders may actually be variations of a single disease.

Family History

Bipolar disorder frequently occurs within families, although genetic factors account for only about 60% of cases. Family members of patients with bipolar disorder also have a higher than average incidence of other psychiatric problems. They include schizophrenia, schizoaffective disorder, anxiety disorders, attention deficit hyperactivity disorder (ADHD), and major depression.

Miscellaneous Factors Associated with Bipolar Disorder

Seasons. A higher incidence of bipolar disorder occurs in people who were born in the winter and in those who had experienced complications around the time of birth. An interesting study of bipolar adults found a correlation between winter birth and the presence of lesions (injured areas) deep in the brain, suggesting that an infection or another environmental assault affected them before birth.

The time of the year appears to play a role in the risk for specific episodes. Mania is more likely to occur in the summer and depressive episodes from October through May (which is different from seasonal affective disorder, a depressive disorder that only occurs in darker months).

Socioeconomic Status. Bipolar disorder is more prevalent among people with a higher socioeconomic status. The rate of the disorder is estimated to be 10 to 20 times higher among people in the creative arts than in the general population.

Loss of a Parent. Children who lose a parent early in life also appear to be more likely to develop bipolar disorder when they become adults.

WHAT CAUSES BIPOLAR DISORDER?

No single cause may ever be found for bipolar disorder. Instead, a combination of biologic, genetic, and environmental factors appears to trigger and perpetuate the chemical imbalances in the brain that shape this complex disorder. Among the biologic factors observed or considered in bipolar disorder, as detected by use of imaging scans and other tests, are the following:

- Oversecretion of cortisol, a stress hormone.
- Excessive influx of calcium into brain cells.
- Abnormal hyperactivity in parts of the brain associated with emotion and movement coordination and low activity in parts of the brain associated with concentration, attention, inhibition, and judgment.
- A superfast "biologic clock" (a tiny cluster of nerves called the supra chiasmatic nucleus or SCN). The SCN is located in the hypothalamus (in the center of the brain) and it regulates a person's circadian rhythm, the daily cycle of life, which influences sleeping and waking.

Biologic and Genetic Factors Shared with Other Disorders

The genetics of bipolar disorder are the most intensively studied of all psychiatric diseases. Multiple genes, involving several chromosomes, have been linked to its development. Bipolar disorder also may share these genetic factors with other disorders, including schizophrenia, epilepsy, and panic disorder. It is not clear if some of these disorders are variations of a single disease or separate disorders.

Bipolar Disorder and Schizophrenia. Researchers have been investigating whether common biologic factors are involved with schizophrenia, severe bipolar disorder, and other psychoses.

Schizophrenia and bipolar disorder often show up in the same family. Researchers are identifying a number of common genetic and biologic pathways that they both share. Some examples of studies comparing biologic differences and similarities include the following:

- Genetic abnormalities for both diseases appear on many of the same chromosomes.
- Pathways of the neurotransmitter dopamine appear to be important in both illnesses. (A neurotransmitter acts as a chemical messenger between nerve cells.)
- Blood levels of reelin, a protein in the brain, may be useful as markers for both schizophrenia and bipolar disorder, although levels vary between the two diseases. (Reelin is a protein that is important for information processing.)
- Elevated levels of vesicular monoamine transporter (VMAT2) have been observed in the brainstems of patients with both bipolar disorder and schizophrenia. VMAT2 is a protein in the brain that regulates the transport of important neurotransmitters. The distribution of this protein in the brain, however, differs between the two diseases.
- In one study of people with bipolar disorder, the left side of the hippocampus was significantly larger than it was on the right. In patients with schizophrenia the hippocampus' volume was decreased. (The hippocampus is located deep in the brain and stores memory.)

Bipolar Disorder and Epilepsy. Neurotransmitters called gamma aminobutyric acid (GABA) and norepinephrine have been implicated in mania.

- GABA helps prevent nerve cells from over-firing.
- Norepinephrine is a hormone that involves stress.

Some research has associated similar biologic mechanisms in patients with epilepsy and bipolar disorder. As in epilepsy, the more episodes a bipolar disorder patient experiences early in the course of the disease, the more frequent and severe later episodes will be. Antiseizure agents, in fact, can play an important role in the treatment of bipolar disorder.

Panic Disorder and Bipolar Disorder. Researchers are also studying the common biologic and genetic factors between panic disorder and bipolar disorder. While specific genes have not yet been identified, some researchers studying these illnesses now believe that they may represent different forms of a shared, complex condition.

Viruses

The high rate of winter births in those who develop bipolar disorder (as well as schizophrenia) has encouraged researchers to look at infectious agents as a possible cause or trigger of these mental disorders.

Borna Virus. The Borna virus is among the infectious agents being intensively studied. This virus is known to cause serious central nervous system injuries in animals, but not in people. A few studies using sensitive blood testing, however, have detected strong evidence of the infection in psychiatric patients. Some researchers believe that the virus may cause subtle changes in the human brain (in contrast to the more dramatic inflammation seen in animals) leading to a range of mental illnesses. It should be noted, however, that other research has not supported the association. Some researchers argue that psychiatric illnesses may suppress the immune system, making some individuals more susceptible to infection by the Borna virus or other microbes.

Herpes Simplex. Another possible viral link under study is herpes simplex virus 2 (HSV-2). Adult children of mothers with HSV-2 prior to delivery may have a greater risk of developing bipolar disorder and other psychoses, according to research published in 2001.

HOW SERIOUS IS BIPOLAR DISORDER?

Risk for Suicide and Overall Mortality Rates

According to a long-term 2002 study, bipolar patients had higher mortality rates from suicide, heart problems, and death from all causes than those in the general population. Patients who obtained treatment, however, experienced significant improvement in survival rates, including deaths from suicide and heart disease. (There is a known connection between heart disease and major depression. In this study, patients treated for major

depression did not have a lower mortality rate from heart disease.)

The risk for suicide is very high in patients who suffer from bipolar disorder and who do not receive medical attention. Between 10% and 15% of patients with bipolar disorder I commit suicide, with the risks being highest during episodes of depression or mixed mania (simultaneous depression and mania). Some studies have suggested that the risk for suicide in bipolar disorder II patients is even higher than it is for those with bipolar disorder I or major depressive disorder. Patients who also suffer from an anxiety disorder, also are at greater risk for suicide. (Rapid cycling, although a more severe bipolar disorder variation, does *not* appear to increase the suicide risk in patients with bipolar disorder.)

Many pre- and early adolescent children with bipolar disorder are more severely ill than are adults with the disease. According to a 2001 study, 25% of children with bipolar disorder are seriously suicidal. They have a higher risk for mixed mania, multiple and frequent cycles, and a long duration of illness without well periods.

Thinking and Memory Problems

Studies suggest that patients with bipolar disorder may have varying degrees of problems with short- and long-term memory, speed of information processing, and mental flexibility. Such problems persist even between episodes. They tend to be more severe when a person has more manic episodes. Medications used for bipolar disorder could be responsible for some of these abnormalities, although some evidence suggests that such traits may have a biologic basis. These mental difficulties may make it harder for these patients to comply with medications or to participate in complex psychotherapies.

Behavioral and Emotional Effects of Manic Phases on the Patient

A small percentage of bipolar disorder patients demonstrate heightened productivity or creativity during manic phases. More often, however, the distorted thinking and impaired judgment that are characteristic of manic episodes can lead to dangerous behavior, including the following:

- Spending money with reckless abandon, causing financial ruin in some cases.
- Angry, paranoid, and even violent behaviors.
- Openly promiscuous behavior.

Often such behaviors are followed by low self-esteem and guilt, which are experienced during the depressed phases. During all stages of the illness, patients need to be reminded that the mood disturbance will pass and that its severity can be diminished by treatment.

Substance Abuse

Cigarette smoking is prevalent among bipolar patients, particularly those who have frequent or severe psychotic symptoms. Some experts speculate that, as in schizophrenia, nicotine use may be a form of self-medication because of its specific effects on the brain; further research is necessary.

Up to 60% of patients with bipolar disorder abuse other substances (most commonly alcohol, followed by marijuana or cocaine) at some point in the course of their illness.

The following are risk factors for alcoholism and substance abuse in bipolar patients:

- Having mixed-state episodes rather than ones of pure mania.
- Being a man with bipolar disorder.

Effects on Loved Ones

Patients do not manifest their negative behaviors (e.g., spending sprees or even becoming verbally or physically aggressive) in a vacuum. They have a direct effect on others around them. It is very difficult for even

the most loving of families or caregivers to be objective and consistently sympathetic with an individual who periodically and unexpectedly creates chaos around them.

Many patients and their families, therefore, cannot admit that these episodes are part of an illness and not simply extreme, but normal, characteristics. Such denial is often strengthened by patients who are highly articulate and deliberate and can intelligently justify their destructive behavior, not only to others, but also to themselves.

Often family members feel socially alienated by the fact of having a relative with mental illness, and they conceal this information from acquaintances. (This is particularly true if the patient is female and lives away from home.) People with more education are more likely to feel ostracized by their acquaintances than are those with less education.

Economic Burden

The economic burden of bipolar disorder is significant. In 1991, the National Institute of Mental Health estimated that the disorder cost the country \$45 billion, including direct costs (patient care, suicides, and institutionalization) and indirect costs (lost productivity and involvement of the criminal justice system). In spite of the obvious need for professional help, access to medical therapies is not always available for patients with bipolar disorder. In one major survey, 13% of patients had no insurance and 15% were unable to afford medical treatment.

Association with Physical Illnesses

People with mental illness have a higher incidence of many medical conditions, including heart disease, asthma and other lung problems, gastrointestinal disorders, skin infections, diabetes, hypertension, migraine headaches, hypothyroidism, and cancer. Bipolar patients are also less likely to receive medical care than people without mental disorders. Substance abuse, including smoking, alcoholism, and drug abuse, also contributes to many of these problems as well as reduced access to care. Medications used for bipolar disorder can also increase the risk for medical problems.

However, people with bipolar disorder and other mental illness have a higher risk for a number of these conditions independent of these factors.

Diabetes. Diabetes is diagnosed almost three times more often in people with bipolar disorder than it is in the general population. A 2002 study reported that 58% of bipolar patients were overweight, with 26% meeting the criteria for obesity. Being overweight is a significant risk factor for diabetes and so it may be the common factor in both diseases. Drugs used to treat bipolar also pose a risk for weight gain and diabetes. Common genetic factors have also been implicated in diabetes and bipolar disorder, including those causing a rare disorder called Wolfram syndrome and those that regulate carbohydrate metabolism.

Migraine Headaches. Migraines are common in patients with a number of mental illnesses, but they are particularly common among bipolar II patients. In one study, 77% of bipolar II patients had migraines while only 14% of bipolar I patients had this headache, suggesting that different biologic factors may be involved with each bipolar form.

Hypothyroidism. Hypothyroidism (low thyroid levels) is a common side effect of lithium, standard treatment for bipolar. However, evidence also suggests that bipolar patients, particularly women, may be at higher risk for low thyroid levels regardless of which medications they use. It may in fact be a risk factor for bipolar disorder in some patients.

HOW IS BIPOLAR DISORDER DIAGNOSED?

Bipolar disorder is more prevalent than was previously thought, but this illness, particularly bipolar disorder II, is still poorly recognized in the family-practice setting. It is estimated that only one-third of affected people are

accurately diagnosed.

Ruling Out Similar Conditions

When making a diagnosis of bipolar disorder, it is important that the physician rule out other conditions that may be causing symptoms of bipolar disorder.

Distinguishing Mania from Normal Euphoria or Joy. A major difficulty with a diagnosis of bipolar disorder is the tendency for a patient to be unable to recognize his or her own condition, particularly when in the manic state. The patient often denies his or her symptoms, which may be perceived as positive feelings. The physician should take a careful and complete history of any and all episodes of depression, mania, or both. Hypomania, the less severe variant of mania, may be particularly difficult to distinguish from normal joy or euphoria. It can often be differentiated by the following characteristics:

- Hypomania persists for at least four days.
- With hypomania most patients are easily distracted and overly talkative.
- With hypomania patients tend not to function very well.

Distinguishing Unipolar from Bipolar Depression. People with bipolar disorder are more likely to seek help because of a depressive episode. Indeed, about 16% of people with bipolar disorder do not have a manic episode until they have experienced three or more depressive episodes. In such cases, the condition is often diagnosed as major depression. An accurate diagnosis is important because bipolar disorder patients who are inappropriately medicated solely with antidepressants have a higher incidence of rehospitalization than do other bipolar disorder patients.

Bipolar disorder should be suspected in patients who have been treated for depression and who had an initial fast and good response, which was followed by failure. Furthermore, they were then resistant to other antidepressants.

A family history of manic-depressive illness may make a physician suspicious, but a diagnosis of bipolar disorder cannot be established until a manic or hypomanic episode has occurred. Bipolar II patients and those with depressive mixed state are more likely to be misdiagnosed with depression. [For symptoms of mixed states and a comparison between unipolar and bipolar depression see *Box, Symptoms of Bipolar Disorder.*]

Attention Deficit Hyperactive Disorder (ADHD). Children or adolescents with manic-depressive illness may be inappropriately diagnosed with attention-deficit hyperactivity disorder. ADHD and bipolar disorder often cause inattention and distractibility, and the two disorders may be difficult to distinguish, particularly in children. In some cases, ADHD in children or adolescents can even be a marker for an emerging bipolar disorder. The primary way to differentiate bipolar disorder from ADHD is by the presence of a manic or hypomanic episode, which occurs in patients with bipolar disorder but not with ADHD. Most children with bipolar will also respond to the drug valproate, which does typically work for ADHD. [For more information, see, *Attention-Deficit Hyperactivity Disorder.*]

Schizophrenia. Severe manic episodes that include delusions and hallucinations may be easily confused with schizophrenia. (African-American men, for instance, are more likely to be diagnosed with schizophrenia than with bipolar disorder.) The key factors that distinguish bipolar disorder from schizophrenia are the following:

- The presence of one or more manic or hypomanic episodes in bipolar disorder, but not in schizophrenia.
- A flat emotional expression, with no variability in the voice, among schizophrenics, while people with bipolar disorder are typically very expressive.

Substance Abuse. Up to 60% of bipolar disorder patients abuse alcohol and drugs at some point during their illness. Both diagnosis and treatment are difficult in such cases, since substance abuse is often a method of self-treatment, and withdrawal can produce symptoms of mania or severe depression. The effects of cocaine in a heavy user can also produce abnormal mood swings that closely resemble those of bipolar disorder.

Other Causes of Mood Swings. Other conditions that can cause mood swings include the following:

- Thyroid disorders. Hypothyroidism may be common in bipolar patients, particularly in women. (This condition can be identified with a blood test).
- Adrenal disorders (e.g., Addison's disease or Cushing's syndrome).
- Vitamin B12 deficiency.
- Certain neurologic disorders (e.g., Huntington's disease, epilepsy, brain tumors, encephalitis, or multiple sclerosis).
- A number of medications, including corticosteroids and certain drugs used to treat anxiety and Parkinson's disease can cause mood swings.

Laboratory Tests

The following tests may be helpful:

- Patients should be tested for drugs or alcohol if the physician suspects that they have been using these substances.
- Blood tests for thyroid function should also be taken.

Imaging Tests

Noninvasive imaging tests of the brain using magnetic resonance imaging (MRI) and positron-emission tomographic (PET) scans are being used in clinical trials for detecting abnormalities in the brain that might identify bipolar disorder and test the effectiveness of treatments.

WHAT ARE THE GENERAL GUIDELINES FOR TREATING BIPOLAR DISORDER?

General Goals of Therapy

Bipolar disorder is a recurrent disease. However, its course is unpredictable. The major goals of treatment, then, are the following:

- To treat and reduce the severity of acute episodes of mania or depression when they occur.
- To reduce the frequency of episodes.
- To avoid cycling from one phase to another.
- To help the patient function as effectively as possible between episodes.

First, the physician will try to determine conditions that might have precipitated the attack and identify any accompanying medical or emotional problems that might interfere with or complicate treatment.

Challenges of Bipolar Treatment

The treatments for bipolar disorder, while very effective, pose some specific challenges for the patient:

- Because the mood variations in bipolar disorder are not predictable, it is sometimes difficult to tell if a patient is responding to treatment or naturally emerging from a bipolar phase.
- A patient with bipolar disorder is not always reliable in reporting the state of the illness to the physician.
- The patient is likely to need more than one medication during the course of the disease. This increases the risk for distressing side effects. Noncompliance is common.
- Patients often have more than one disorder and need different drugs for each disorder. Such agents may interact with drugs used to treat bipolar disorder or increase side effects. For example, children with bipolar disorder have a higher risk for attention deficit-hyperactivity disorder, which is treated with

- stimulants that can complicate treatment.
- Family members who have not been educated about the disorder may undermine the treatment.
- Treatment strategies for children and the elderly have not been intensively studied and have not been clearly defined.
- Treatments may be costly.

Specific Drugs and Other Treatments Used in Bipolar Disorder

The following are the treatment options for most patients with bipolar disorder, depending on the bipolar disorder phase or episode. Patients should understand that, even with aggressive therapy, either mania or depression recurs in almost three-quarters of patients.

Drugs Used in Bipolar Disorder. Mood stabilizing drugs are the mainstay for patients with bipolar disorder. They are defined as drugs that are effective for acute episodes of mania and depression and that can be used for maintenance. The currently available first-line mood stabilizers are lithium and valproate. Both drugs stimulate the release of the neurotransmitter glutamate, although they appear to work through different mechanisms. Other drugs may also be used.

- Lithium. Lithium has been used for years for bipolar disorder. It remains the best drug for people with pure mania characterized by euphoria and pure depression. And, although imperfect, it is also an effective long-term drug for many patients with other bipolar subtypes.
- Antiseizure Agents. Valproate is an anti-seizure agent that is effective for many patients with mania, rapid-cycling, and mixed states, as well as for patients who are also substance abusers. Carbamazepine (Tegretol, Carbatrol) is usually the second anti-seizure medication of choice. Lamotrigine (Lamictal), a newer antiseizure drug, is proving to be an effective mood-stabilizer and, in fact, is more effective for depressive episodes than is lithium. It may be particularly helpful for patients with rapid cycling and bipolar II disorder, in whom depression remains problematic after taking other mood stabilizers. Other anti-seizure agents used or investigated for bipolar include gabapentin (Neurontin), zonisamide (Zonegran) and topiramate (Topamax). To date, it is not clear if these newer agents are useful for the treatment of acute mania.
- Atypical Antipsychotics. Agents known as atypical antipsychotics also have mood stabilizing properties. Clozapine (Clozaril) was the first atypical antipsychotic. Newer agents include risperidone (Risperdal), olanzapine (Zyprexa), quetiapine (Seroquel), ziprasidone (Zeldox), and others.

Such agents may be used in combination with each other. Additional drugs, such as conventional antipsychotics, antidepressants, anti-anxiety drugs, or experimental agents are used as necessary.

Electroconvulsive Therapy. Electroconvulsive therapy is a very effective treatment that may be administered in certain patients for acute episodes or for maintenance.

Non-Medical Treatments. In addition to medical treatments, psychologic therapies and sleep management are also extremely critical components of bipolar disorder treatment to reduce symptoms and to help the patient manage and even prevent relapse.

Treatment Guidelines for Acute Manic Episodes

Step 1. Determine the Need for Hospitalization and Eliminate Triggers. The first step in treating an acute manic episode is to rule out any life-threatening conditions and eliminate any triggers, such as antidepressants or other mood elevators.

Patients often require hospitalization at the onset of acute mania. The need for hospitalization depends on a number of factors, including the following:

- Whether the patient is at risk for suicide or for harming others.
- The availability of social and emotional support at home.

Step 2. Control Symptoms of Acute Manic with a Mood Stabilizer. Physicians must often try different agents to control a manic episode, usually adding them one at a time to the regimen if the current drugs are not effective. It may take several weeks for a mood stabilizer to be effective and other agents may be needed.

The following is an example of a stepped approach recommended by some experts:

- Initiating a mood-stabilizing drug is the critical first step. Either valproate or lithium is the standard first agent for most manic episodes. Lithium is effective in 60% to 80% of all hypomanic and manic episodes. Valproate is not usually preferred, however, for patients with multiple manic episodes, mixed episodes, and rapid cycling. Carbamazepine, another anti-seizure agent is a good alternative. Combinations of these mood stabilizers may be used if the patient does not respond to a single agent.
- If the patient does not respond fully within a week, atypical antipsychotics may be added to one or more mood stabilizers. Atypicals include olanzapine (Zyprexa), risperidone (Risperdal) and quetiapine (Seroquel). Olanzapine, in fact, has been approved as sole therapy for manic episodes. It has not been studied for very long, however and may have more side effects (importantly weight gain) than does valproate. Clozapine (Clozaril), the oldest atypical agent, is also effective but it is not generally used because of its potential for severe side effects and the need for weekly monitoring of white blood cell counts.
- Finally, the physician may consider adding newer anti-seizure agents, such as lamotrigine, topiramate, or gabapentin.

Step 3. Addition of Other Treatments. Other treatments may be added to speed recovery, treat any psychosis, and achieve remission. They include any of the following:

- Standard antipsychotic drugs (also called neuroleptics), such as haloperidol (Haldol). These agents may be used for acute mania. They can cause severe side effects, however, particularly those known as extrapyramidal effects, which disrupt motor control. They are not generally used on a long-term basis for those with bipolar disorder.
- Benzodiazepines, such as clonazepam (Klonopin) or lorazepam (Ativan), are anti-anxiety agents that may be particularly beneficial agents to add if the patient is experiencing severe mania.
- Electroconvulsive therapy. This treatment helps patients who do not respond to medication and may even be life-saving in elderly patients with severe late-onset mania.

Step 4. Terminate Some Drug Treatments. Drugs may be stopped under the following circumstances:

- When side effects are intolerable.
- When the patient does not respond to the maximum dose.
- When the patient improves and recovery is sustained. In such cases, the neuroleptic or benzodiazepine is slowly withdrawn and only the mood-stabilizing drug is continued.

Step 5. Continuation of Mood Stabilizers. Mood stabilizers are typically continued for about eight weeks, unless the patient shows signs of shifting to another mood state. If the patient remains stable at that time, the physician may decide to continue maintenance treatment or to gradually withdraw medications.

Treatment Guidelines for Depressive Episodes

Depressive episodes pose a particular challenge. They are a significant cause of suffering and yet the use of standard antidepressants poses a significant risk for triggering mania. Their effectiveness is also questionable. In fact, depressive episodes are so difficult to treat that some experts advise patients who do not respond to mood stabilizers to simply expect to endure the depressive episode for about two to three months. [For more information, see What Are the Major Drugs Used for Bipolar Disorder, below.]

First Choice: Mood Stabilizers. Mood stabilizers are first-line treatment for depressive episodes. (About half of all patients with bipolar disorder and depressive episodes will respond to this treatment.) Lithium and valproate are the standard mood stabilizers. One study suggested that increasing the dosage of valproate may help avoid the need for antidepressants. Of note, evidence suggests that lamotrigine, one of the anti-seizure agents, may be an especially beneficial as a mood stabilizer for depressive episodes.

Subsequent Choices: Antidepressants. If improvement does not occur within two to four weeks, then an antidepressant may be added.

The first choices are bupropion (Wellbutrin) or one of the selective serotonin reuptake inhibitors (SSRIs), such as paroxetine (Paxil) or sertraline (Zoloft). These agents are similar in effectiveness and also for risks for switch-back to a manic state (12% to 28%). Patients might try other antidepressants if mood does not improve. Such antidepressants are typically either a monoamine oxidase inhibitor (MAOI), such as tranylcypromine (Parnate), or a newer antidepressant called venlafaxine (Effexor).

It should be noted that a number of studies have found no additional benefits from antidepressants. A 2002 study found no difference in the duration of depression among patients regardless of whether or not they were taking the medications. One 2002 study suggested, however, that patients taking antidepressants for depressive episodes that followed an episode-free state might expect good results. In such cases response rates were 63%. On the other hand, only 28% of patients whose depression had followed a manic or hypomanic episode responded to antidepressants. In addition, their chances of switching back into a manic state were greater, whether or not they were taking an antidepressant or a mood stabilizer.

Any patient on antidepressants who develops symptoms of hypomania should stop taking them, since this is often a sign of impending mania. All antidepressants should be tapered after the mood has been stabilized for a month. Of some concern was a study reporting a paradoxical response in which manic symptoms developed in some patients when they discontinued antidepressant therapy, even though they were also receiving mood stabilizers.

Cognitive-Behavioral Therapy. Cognitive-behavioral therapy (CBT) programs may help patients endure depressive episodes by developing ways to manage negative thoughts and behaviors.

Other Treatments. Electroconvulsive therapy (ECT) is another option for depression that does not respond to less intense approaches. Other drugs sometimes used for depressive episodes include antipsychotic medication for severely depressed and delusional patients. Small studies indicate that a subgroup of patients may respond to thyrotropin-releasing hormone, a substance that regulates thyroid hormones.

Treatment Guidelines for Mixed Episodes and Rapid Cycling

At one time, patients with rapid cycling were treated with a single drug, but now treatment typically involves the use of three or four drugs. There are different approaches:

- Mixed states and rapid cycling tend to be more resistant to lithium, and so valproate in combination with other agents is usually a reasonable choice. One approach, for example, uses valproate first, followed by carbamazepine, and then a combination of carbamazepine and lithium.
- The anti-seizure drug lamotrigine is proving to be especially effective for rapid cyclers, particularly those who have severe depression. Other newer generation anti-seizure agents may also be useful for rapid cyclers.
- Atypical drugs, such as clozapine, may help some patients.
- One biological mechanism involved with rapid cycling is an excessive influx of calcium into brain cells. Cardiovascular drugs called calcium channel blockers, such as nimodipine, may be beneficial for ultra-rapid cycling.
- In some cases, levothyroxine, a synthetic derivative of the thyroid hormone T4 (thyroxine), has helped stabilize rapid-cycling patients. Because of possible problems with long-term use of thyroid hormone, however, other agents should be tried first.
- Electroconvulsive therapy can be useful in emergency situations.

In addition, other measures should be taken:

- Patients should avoid anti-anxiety drugs, alcohol, caffeine, and stimulants.
- Patients should avoid exposure to bright light.
- All efforts should be made to help the patient sleep normally.

Treatment Guidelines for Maintenance

Drugs Used During Maintenance. Relapse occurs in most patients after treatment of acute attacks, and patients who are at high risk for recurring episodes should consider life-long maintenance therapy, generally using mood-stabilizing agents.

- Lithium is a first-line mood stabilizer used in maintenance therapy. The anti-epileptic agent valproate is also a first-line agent. In general, the two are equal in effectiveness, although valproate may be better for patients who have had multiple manic episodes. There are some differences in side effects but the drop-out rates between the drugs are similar.
- Carbamazepine, another anti-epileptic agent, is a third alternative.
- The atypical antipsychotic drugs clozapine (Clozaril), olanzapine (Zyprexa), and risperidone (Risperdal) are also proving useful for maintenance, particularly in combination with mood stabilizers.

The general recommendations for maintenance therapy with lithium are as follows:

- The earlier lithium is started in the disease process, the more effective it is. Studies are showing that patients on long-term lithium therapy have survival rates comparable to the general population, but those who permanently drop out of therapy have significantly lower survival rates. In one study, patients who stopped taking it increased their risk of suicide in the first year by 20-fold.
- Lithium is still effective for patients who discontinue and then restart treatment later on. In such cases, however, there may be a greater need for drug combinations. In addition, patients who stop and start again may be at higher risk for hospitalization than those who use the drug continuously.
- For those who want to stop, a gradual discontinuation (over 15 to 30 days) may help to delay recurrence. Stopping it quickly poses a high risk for relapse and even for suicide.

Electroconvulsive Therapy. Some studies are finding that maintenance electroconvulsive therapy (ECT) may be helpful for those who do not respond to medications. In one study of patients with bipolar disorder, those who had intractable recurrent episodes were maintained on monthly ECT treatments for more than a year and a half. Without ECT, those patients spent an average of almost half a year in the hospital, suffering at least three episodes annually. After ECT, all the rapid cyclers achieved full or partial remission.

Guidelines for the Treatment of Pregnant Patients with Bipolar Disorder

Information on clinical care of pregnant women with bipolar disorder remains very limited. In fact, in one survey, almost half of women with bipolar disorder were discouraged by their physicians from becoming pregnant. Nevertheless, after careful counseling about medications, possibilities for relapse, and disease severity, nearly two-thirds of them decided to attempt pregnancy.

Risks for Bipolar Episodes. Some studies suggest the following risks for bipolar episodes during and after pregnancy:

- In women who discontinue lithium during pregnancy, the chance for recurrence of bipolar disorder is the same as in non-pregnant women, which is over 50%.
- Pregnant women with bipolar disorder are at particularly high-risk for recurrence in the postpartum period. In one study, symptoms recurred in 74% of women after delivery, and another 20% were hospitalized within 90 days after giving birth. The risk for depressive or mixed states is particularly high.

Drugs for Bipolar and Pregnancy. It is not ethical to test drugs during pregnancy, so all known effects of bipolar agents are reported anecdotally. It is well known, however, that most of the mood stabilizers used for bipolar disorder carry a high risk for the fetus if taken, particularly in the first trimester, by pregnant women. New agents are under investigation, but data is limited. The following are some reports on the effects of certain drugs during pregnancy:

- Lithium. When mothers used lithium in the first three months of pregnancy, some studies reported a higher incidence of a certain type of heart defect and other birth abnormalities in the baby. More recent

studies, however, indicate that it may pose fewer dangers for the fetus than previously believed. Physicians may now prescribe lithium at the time of delivery with some confidence that it will not harm the mother or baby. Mothers who are taking lithium should not nurse their babies, since lithium is concentrated in breast milk.

- Antiseizure Agents. Both valproate and carbamazepine greatly increase the risk for physical malformations, for developmental delay, and for spina bifida in babies. They appear to have minimal effect on breast feeding however. Evidence to date suggests that lamotrigine, a newer anti-seizure agent, may not pose the same risks, but data are limited.
- Atypical Antipsychotics. Small studies have suggested that olanzapine does not increase the risk for birth defects. However, it does pose a great risk for excess weight gain that could be unhealthy during pregnancy. Less is known about the effects of other atypical agents during pregnancy.

Taking mood stabilizers at the time of delivery has been shown to significantly reduce the risk of recurrence of episodes after the baby is born. However, caution is still advised.

Electroconvulsive Therapy (ECT). In spite of its bad press, ECT appears to be very beneficial for bipolar disorder women who become pregnant. The patient should discuss this option with her physician. [See What Are Electroconvulsive Therapy And Other Procedures for Bipolar Disorder?]

Treatment Guidelines for Children and Adolescents

There are few studies on the optimal treatment of bipolar disorder in children and adolescents. The drugs used for bipolar disorder have considerable side effects, which may be severe in younger people. Parents should consider the potential risks and benefits of treatment for their children.

The drugs that have been most studied for this population are lithium and valproate. Some evidence suggests that larger rather than smaller doses of valproate or lithium may be more effective in children and adolescents with bipolar disorder. However, side effects of these drugs in children may be especially problematic, including severely impaired thinking, acne, and increased urination (caused by lithium) and menstrual irregularities and polycystic ovary syndrome (from valproate).

Atypical antipsychotics, especially olanzapine (Zyprexa) or risperidone (Risperdal), are being investigated in combination with mood stabilizers. They may be helpful for young people with severe aggression. These drugs can cause severe side effects, including significant weight gain. [For specific information on all of the drugs, see the section What Are the Major Drugs Used for Bipolar Disorder?]

Electroconvulsive therapy (ECT) may be effective and safe in children and adolescents. The side effects (e.g., amnesia, fractures, and panic) associated with older ECT techniques have been greatly reduced. Given the significant side effects of bipolar drugs, parents should discuss this technique with their physicians.

WHAT ARE THE MAJOR DRUGS USED FOR BIPOLAR DISORDER?

Lithium

Lithium (Carbolith, Duralith, Lithobid, Lithizine, Eskalith, Lithane) is one of the standard mood stabilizing drugs for bipolar disorder. Lithium is extremely beneficial for most patients and it significantly reduces the rate of hospitalizations in bipolar disorder patients. Some studies report the following advantages:

- Lithium is effective in 60% to 80% of all hypomanic and manic episodes. (Valproate may be better in patients with multiple manic episodes, mixed episodes, and rapid cycling.)
- It helps to prevent relapses.
- It has a beneficial effect on psychosocial functioning.
- One study indicated that lithium reduced the risk for suicide regardless of its effects on stabilizing mood.
- One small study suggested that lithium may act directly on the nerve clusters affecting the circadian

rhythm and slow down the cycle of this "biologic clock." (There is some evidence that bipolar patients have a faster biologic clock.)

- Despite previous concerns, lithium remains effective for most patients even if they have discontinued taking it and wish to restart treatment.

Administration of Lithium. Lithium may take weeks to become totally effective, so patients should not expect an immediate response during an acute episode. Physicians may take different approaches to administering the drug:

- Some physicians initially administer lithium in two low doses and gradually increase the dosage over time until an effective (therapeutic) level is achieved.
- Another approach is to administer a higher dose initially and measure blood levels of the drug after 24 hours. The physician uses this information combined with a chart called a nomogram to calculate the doses most likely to be therapeutic on a regular basis.

In either case, lithium levels should be monitored regularly. Side effects and toxicity can occur at therapeutic levels or at those only slightly higher than desired. Blood tests that measure drug levels should be conducted frequently during acute attacks and about every three months during maintenance therapy.

Toxic Effects. Minor toxic reactions include the following:

- Trembling hands.
- Nausea.
- Increased urine output.
- Blurred vision.
- Some loss of coordination.

More severe reactions, which occur at higher blood levels, are the following:

- Vomiting.
- Convulsions.
- Uncontrolled jerky movements in arms and legs.
- Stupor.
- Coma.

Very high blood levels of lithium can be fatal.

If toxicity occurs, drugs should be stopped immediately and one or more of the following steps taken, depending on the severity:

- Patients are given fluids and drugs to increase excretion of lithium salts.
- Gastric lavage, a procedure that rinses the stomach may be used to treat very recent overdoses.
- Hemodialysis, a procedure that filters lithium out of the blood, may also be performed in severe cases.

Long-Term Side Effects. Even for patients who do not experience a toxic response, long-term use of lithium is not without problems. Some patients may experience the following:

- An unpleasant taste in the mouth.
- Hair loss.
- Weight gain. In one study, 16% of patients gained weight. It is a frequent reason for noncompliance and for relapse.
- Skin eruptions that can resemble acne. (It can worsen psoriasis in patients who also have this condition.)
- Thyroid problems. Up to 20% of patients who take lithium develop symptomatic hypothyroidism, and another 20% to 30% develop hypothyroidism without symptoms.
- An increased risk for diabetes.
- A blunted sexual drive.
- Dulled emotions and mental acuity.

- Memory loss.
- Lack of motor coordination.
- An increased risk for diabetes associated with kidney impairment.
- Reduced sensitivity to light. In some cases, this may slightly affect color recognition. More seriously it can cause problems with night driving. This effect occurs regardless of how long a person has been on the drug. Experts recommend that patients wear sunglasses outside and avoid extensive exposure to bright light.

Drug Interactions. Because lithium is eliminated from the body by the kidneys, any drugs or dietary factors that slow the kidneys' actions may increase lithium blood levels and should be used with great caution. Such drugs include the following:

- Nonsteroidal anti-inflammatory drugs (NSAIDs).
- Thiazide diuretics.
- ACE inhibitors.

There have been reports of interactions between lithium and certain drugs commonly used in combination, including the following:

- Antipsychotics.
- Anticonvulsants.
- Calcium-channel blockers.

It should be noted that the risks associated with these drugs are very low, but caution is needed.

Other Factors that Affect Lithium Levels. In addition to drugs, other factors may affect lithium levels, including the following:

- Seasonal change. For instance, one study of men with bipolar disorder suggested that lithium levels may be higher in summer.
- Menstrual cycle. Lithium levels may drop during the premenstrual phase.
- Weight loss.
- Changes in salt intake.
- Dehydration.
- Diarrhea.
- Patients should be sure to contact their physician if they have any suspicious symptoms or illnesses.

Noncompliance. Noncompliance is common. One study of lithium users found that patients took their medication only 34% of the time. Another reported that nearly a third of patients eventually went off the drug.

Side effects are certainly one reason for noncompliance. Some patients regret the loss of their manic episodes and the exhilaration and creativity that sometimes accompany them. In one small study of artists with bipolar disorder, however, only 25% felt their work had declined, while another 25% found no change in their creative output, and half believed that lithium had improved their output.

It should be strongly noted that this important drug saves lives. And, physicians are confident that lithium, which has been in use for more than 50 years, can be taken safely, even for life, by most patients.

Valproate and Other Anti-Seizure Drugs

Anti-seizure drugs, also called anti-epileptics or anticonvulsants, affect the neurotransmitter gamma aminobutyric acid (GABA), which helps prevent nerve cells from over-firing. They have become alternative treatments for patients who need a mood-stabilizing agent, but who do not fare well with lithium. They may also be used in combination with lithium.

Standard Anti-Seizure Agents.

- Valproate (Depakote), also called valproic acid or divalproex, is now commonly a first option for many bipolar disorder patients. Valproate is more effective than lithium for patients with a history of many manic episodes. In fact, in one study, lithium had no significant effect for these patients. Valproate also helps migraine headaches, a common problem among bipolar patients.
- Carbamazepine (Epilex, Tegretol) is a standard alternative anti-seizure agent used for mood stabilizing.

Either one may be an alternative for patients (especially substance abusers) who do not tolerate or respond to lithium. Both valproate and carbamazepine are comparable to lithium in long-term effectiveness. Evidence is mixed on the whether they pose a higher risk for breakthrough depression, with one 2001 study suggesting that valproate, in higher doses, may actually have anti-depressant properties.

Newer Anti-Seizure Agents. Newer anti-seizure agents under investigation for bipolar include lamotrigine (Lamictal), levetiracetam (Keppra), topiramate (Topamax), and zonisamide (Zonegran). Lamotrigine is the most studied of these agents and is proving to be particularly effective for depressive episodes and rapid cycling. Topiramate is also proving to be a useful agent in combination with mood stabilizers. It may have a particular advantage over others, in that it does not cause weight gain. It is not clear if any of these agents have any effect on acute mania.

General Side Effects. The side effects given here are associated with valproate. Other anti-seizure agents have similar effects and some specific ones of their own. Most are usually minor, occurring early in therapy, and then subsiding. Those of valproate include the following:

- Gastrointestinal problems (nausea, vomiting, heartburn). (In some studies, such side effects occurred initially in half the patients taking valproate.)
- Headaches.
- Visual disturbances.
- Ringing in the ear.
- Hair loss.
- Weight gain (a significant problem with valproate). In one study 23% of valproate-treated patients gained weight. (Other anti-seizure agents, such as topiramate, may actually be helpful for reducing treatment-related weight gain.)
- Agitation.
- Odd movements.
- In women, menstrual irregularities and a higher risk for polycystic ovary syndrome (PCO). (These side effects also appear in women using other anti-epileptic drugs, but the risk for those taking valproate may be higher.)
- Significant for birth defects when taken by pregnant women. (Valproate is, however, the preferred drug for women taking oral contraceptives.)
- Cognitive impairment and symptoms of Parkinson's disease. (One study of patients taking valproate for epilepsy for longer than a year reported these side effects in some patients. They resolved when valproate therapy was discontinued.)

Very serious side effects are rare but include the following:

- Liver damage.
- Convulsions.
- Coma.
- Pancreatitis in adults and children.

Atypical Antipsychotics

Atypical antipsychotics are standard agents for schizophrenia. They are now proving to be beneficial in combination with mood stabilizers for treating mania. These drugs include clozapine (Clozaril) (the first atypical antipsychotic), olanzapine (Zyprexa), risperidone (Risperdal), quetiapine (Seroquel), zotepine (Zoleptil), and ziprasidone (Geodon). Other atypical agents under investigation include aripiprazole (Abilitat) and iloperidone (Zomaril).

Clozapine is useful for rapid cycling, psychosis, and mania, although it has significant side effects and is not usually a first choice among these agents. Olanzapine and risperidone are better tolerated than clozapine and are effective for mania, both in acute and long-term use. Olanzapine was approved in 2000 for acute manic episodes. Others are also showing promise.

Side Effects. Although atypical antipsychotics have fewer severe side effects than standard antipsychotics, many patients fail to comply with regimens containing them. Common side effects include the following:

- Nasal congestion or runny nose.
- Drooling.
- Dizziness.
- Headache.
- Drowsiness. (In some cases, drugs may also cause restlessness and insomnia, however.)
- Constipation.
- Rapid heart beat.
- Difficulty urinating.
- Skin rash.
- Increased body temperature because of reduced sweating. (On the other hand, some may also cause profuse sweating.)
- Mental effects (confusion, short-term memory problems, disorientation, and impaired attention).

Atypicals also have some rare but serious adverse effects, including the following:

- Seizures. (5% risk per year with clozapine. Others pose less of a risk.)
- An increase in weight, a higher cholesterol level, and a greater risk for diabetes, with a subsequent risk for heart disease. Not all atypicals pose the same risks.
- A higher risk of heat stroke.
- Lack of motor coordination and involuntary movements (called extrapyramidal side effects).
- An increase in risk for cataracts and worsening of any existing glaucoma.
- An increase in prolactin levels. Prolactin is a hormone that can cause fluid secretions from breasts in women or impotence in men. Of concern, is a higher risk for breast cancer in women with increased prolactin levels.
- Heart problems, including arrhythmias (associated with a few reports of sudden death with initial usage of the drug). The risk for abnormal heart rhythms appears to be highest with clozapine and olanzapine, moderate with risperidone, and low with quetiapine.
- Agranulocytosis, a potentially life-threatening reduction in certain white blood cells. This complication occurs in about 1% of people taking clozapine, most often within three months of treatment and peaking in the third month. If it hasn't appeared within six months, it most likely will not develop. This complication can be reversed if the drug is withdrawn at once. Older women are at higher risk.

Antidepressants

Antidepressants are sometimes used for depressive episodes in bipolar disorder, but their use is controversial. They can trigger mania in 12% to 28% of patients. In addition, a number of studies report no additional benefits from antidepressants. A 2002 study suggested that they may be helpful for patients whose depression occurs after an episode-free period (rather than after a manic or hypomanic episode.) Specific ones may be beneficial in certain circumstances, in any case. Any patient on antidepressants who develops symptoms of hypomania should stop taking them, since this is often a sign of impending mania. All antidepressants should be tapered after the mood has been stabilized for a month.

Bupropion. The antidepressant bupropion (Wellbutrin) is a unique drug that appears to pose a lower risk for triggering mania than do other antidepressants. Side effects include restlessness, agitation, sleeplessness, headache, rashes, stomach problems, and in rare cases, hallucinations and bizarre thinking. Initial weight loss occurs in about 25% of patients. High doses may cause seizures. This side effect is uncommon and tends to occur in patients with eating disorders (anorexia or bulimia) or those with risk factors for seizures.

Selective Serotonin Reuptake Inhibitors. Serotonin reuptake inhibitors (SSRIs), such as fluoxetine (Prozac),

citalopram (Celexa), sertraline (Zoloft), and paroxetine (Paxil), are being used to treat bipolar depression, but their benefits have not yet been established. They may be useful in patients whose depression does not respond to lithium; they do not appear to be useful as an add-on treatment to lithium. Side effects include the following:

- Nausea and gastrointestinal problems. These effects usually wear off over time.
- Agitation, insomnia, mild tremor, and impulsivity occur in 10% to 20% of people who take SSRIs.
- Dry mouth is common and can increase the risk for cavities and mouth sores.
- Headache.
- Some weight loss during the first few weeks of treatment may occur, but over time patients on maintenance treatment typically return to their pretreatment weight.
- Sexual dysfunction.

Monoamine Oxidase Inhibitors (MAOIs). Drugs known as monoamine oxidase inhibitors (MAOIs), particularly tranylcypromine (Parnate) are recommended for depression that does not respond to the newer antidepressants or SSRIs. MAOIs interact with certain foods to cause severe hypertension. Such foods have a high tyramine content and include aged cheeses, most red wines, vermouth, dried meats and fish, canned figs, fava beans, and concentrated yeast products. MAOIs can also have severe interactions with certain drugs, including some common over-the-counter cough medications. In such cases, severe hypertension or toxic reactions can occur. It is very important, therefore, that the patient discusses with the physician any other medications being taken.

Venlafaxine. Venlafaxine (Effexor), another unique antidepressant, may also be used in severe cases of depression that do not respond to other treatments.

Calcium-Channel Blockers

Calcium-channel blockers are agents commonly used for angina and high blood pressure. They also have nerve-protecting properties. Several studies have reported that at least one of these agents--verapamil (Calan, Isoptin, Verelan)--has anti-manic and possibly mood-stabilizing effects. In a 2002 study, all patients with mania or hypomania reported at least a 50% improvement. In addition, 78% of patients with mixed states reported that mania improved and 39% of patients with depression and no mania or hypomania improved. Other calcium channel blockers, such as nimodipine (Nimotop), may be beneficial for ultra-rapid cycling. Nimodipine has been shown to reduce hypomania and it is particularly effective when added to carbamazepine.

These agents do not cause mental dysfunction, sedation, or weight gain as do other bipolar agents. They may be safer during pregnancy and breastfeeding. Their side effects can include fluid accumulation in the feet, constipation, fatigue, impotence, gingivitis, flushing, and allergic symptoms. Overdose can cause a severe drop in blood pressure. Note: Grapefruits and Seville, or sour, oranges, boost the effects of calcium-channel blocking drugs. (Regular oranges do not appear to pose any hazard.)

WHAT ARE ELECTROCONVULSIVE THERAPY AND OTHER PROCEDURES FOR BIPOLAR DISORDER?

Electroconvulsive Therapy

Commonly called shock treatment, electroconvulsive therapy (ECT) has received bad press since it was introduced in the 1930s. Over the years it has been refined, however, and may now even be safer than lithium. It may be particularly beneficial for the following patients:

- Patients who need immediate stabilization of their condition and who cannot wait for medications to become effective.
- Most patients with mania. (It may be particularly important for elderly patients with severe mania.)
- Patients who suffer suicidal thoughts and guilt during the depressive phase.
- Patients who simply prefer ECT.

- Pregnant patients.
- Patients who cannot tolerate drug treatments.
- Patients with certain types of heart problems.
- Young patients.

In a review of studies, about 80% of ECT-treated patients experienced improvement, and for some, it is the only treatment that works.

The Procedure. Hospitalization is not necessary for the treatment. In general, ECT proceeds as follows:

- A muscle relaxant and short-acting anesthetic are administered.
- A small amount of electric current is sent to the brain, causing a generalized seizure that lasts for about 40 seconds.
- The response to ECT is usually very fast, and the patient often needs less medication afterward.

Side Effects. Side effects of ECT may include temporary confusion, memory lapses, headache, nausea, muscle soreness, and heart disturbances. Administration of the drug naloxone immediately before ECT may help reduce its effects on concentration and some (but not all) forms of memory impairment. Concerns about permanent memory loss appear to be unfounded. One study that used brain scans before and after ECT found no evidence of cell damage. In another small study of teenagers who had undergone ECT for severe mood disorders, only one of 10 reported memory impairment three and one half years after the treatment.

The Biologic Effects ECT on Bipolar Disorder. The precise mechanism by which ECT benefits bipolar disorder patients is not clear.

- Some research is focusing on changes that ECT exerts on the brain's physiology. It may increase the permeability of the blood-brain barrier, produce an anti-seizure effect (similar to the effects of anti-seizure drugs used as mood stabilizers), and reduce blood flow in part of the brain correlated with improved mood.
- Another theory suggests that various hormonal changes that occur during ECT produce the primary benefits, with particular interest in changes in thyroid-related hormones.
- Yet another theory posits that the benefits of ECT stem from its effects on dopamine levels. This neurotransmitter probably plays an important role in bipolar disorder as well as other conditions for which ECT is sometimes recommended, including delusional depression.
- ECT appears to stimulate growth of neurons in the hippocampus (the area in the brain responsible for memory).

Experimental Procedures

Magnetic Therapy. Repeated transcranial magnetic stimulation (rTMS) is also being studied for depression and bipolar disorder. Unlike ECT, this procedure appears not to cause seizures, memory lapses, or impaired thinking. The only side effect reported is a mild headache. One study in patients with unipolar depression found that after one year relapse rates were significantly lower after rTMS than after ECT, although only a few small studies have been conducted using this procedure and it still needs refinement.

Acupuncture. The first study on acupuncture as an add-on therapy for bipolar disorder is currently underway in the US. Some studies have suggested that acupuncture may affect part of the nervous system that regulates the stress response, which might aid patients with bipolar disorder.

WHAT ARE THE PSYCHOLOGIC AND LIFESTYLE APPROACHES TO BIPOLAR DISORDER?

Bipolar disorder is the result of chemical imbalances in the brain and classic psychotherapy has not been effective for these patients. Nevertheless, many newer approaches are proving to be very helpful. In addition, psychological support by trained mental health professionals is essential for all phases of the problem:

- Mental health professionals can educate patients about the disorder and its treatments and help them comply with drug regimens.
- They can monitor the patient's on-going status and intervene early in manic and depressive episodes to reduce the severity of the attack.
- They can help patients adjust to the reality of the illness and to understand the negative consequences of mania. (This is particularly important for patients who avoid treatment because they consider their mania to be positive, creative, and exhilarating.)
- Just as important, therapists can help patients cope with feelings of guilt and remorse that occur in response to their actions during mania.
- Professionals are important in helping patients deal with feelings of imperfection and despair when they acknowledge their illness. These feelings would be difficult enough in a healthy individual, but accompanying depression, which places the patient in danger of suicide, often compounds them.

Cognitive-Behavioral Therapy

Therapists trained in cognitive-behavioral therapy (CBT) may be particularly beneficial for many patients. CBT is a structured, conscious method that aims to help a patient recognize negative thoughts and behavioral patterns and to change them. CBT is known to be helpful for other mood disorders, including depression and anxiety, and small studies are finding that it benefits bipolar disorder patients as well. For example, in a 2003 study, patients who were given mood stabilizers and underwent a CBT program that was specifically designed to prevent relapse experienced fewer and shorter episodes and improved social functioning compared to those on mood stabilizers alone.

Using Cognitive-Behavioral Therapy for Bipolar Disorder. Typical goals of CBT for bipolar disorder patients include the following:

- To learn how to recognize manic episodes before they become full-blown and to change behaviors during an episode.
- To learn how to endure depression by developing behaviors and thoughts that may help offset the negative mood.

Monitoring and Grading Mood. One useful technique is a method for helping the patient predict or recognize an impending episode. This is done using a graph and diary that records and grades the effect of the patient's mental state on energy and physical activity.

There are a number of charts for doing this. With one method the patient makes a time line across the page and a vertical line on the left side of the time line with a range from -5 to +5:

- -5 to -1 indicates the depressive phase. Minus five is the most severe depressive state and requires hospitalization. At this score, the patient's psychomotor responses are almost entirely negative. The patient is unable to function, has no appetite, and can barely get out of bed. As the scale moves up to zero, the depressive state lessens, so that minus one connotes subdued mood with slightly less energy than normal.
- Zero is normal.
- Plus one to five indicates the manic phase. For example, plus one indicates a slightly more active and energetic state than normal. Plus five is the most severe manic state, where the patient is incapable of slowing down, experiences impaired thinking and judgment, and sleeps at least two hours less than normal.

To fill out the graph, the patient takes the following steps:

- Using a diary, the patient describes each day, the mood, and its effect on physical activities.
- Using this information, the patient makes a mark on the scale that roughly reflects each day's mood and its effect on function. The patient then connects the mark with that of the previous day's state.
- The patient also describes any significant emotional or physical events, menstruation, medications, and dosages taken, or any factor that may be relevant in influencing the mood or activities.
- After several months, the therapist and patient may be able to detect a pattern and possibly identify

triggers of bipolar disorder episodes.

- Such information helps the patients to make adjustments that might reduce the severity of mood swings. For example, if a predictor for either manic or depressive episodes is insomnia, the physician might use sleep-inducing methods or medications that might reduce the severity of the emerging mania.

Family Therapy

It is very important that partners, family members, or both should be involved in therapy. Cognitive-behavioral therapy is also useful to help them learn how to accept the condition, the need for medications, and how to protect themselves and the patient financially during manic episodes. In fact, one study indicated that when a spouse of a patient learned ways of coping with the illness, the partner's chances of sticking to a prescribed treatment improved.

Supporting the Patient. Some recommendations for supporting the patient are the following:

- Create a treatment contract as a first step, in which the patient and family agree to specific steps for maintaining emotional stability. If such measures fail, all parties agree on further actions to be taken during an acute episode, including requests for hospitalization.
- Be supportive. Unlike relatives of alcoholic patients who may be encouraged to get tough, relatives of bipolar disorder patients must be strongly supportive because of the high risk for suicide with this disorder. Simply listening attentively and being empathic can help.
- Get the patient to comply with treatment, even if it means threatening a hospitalization if the patient fails to comply.
- Have a hotline number or the telephone number of a psychiatrist authorized to commit the patient and who is willing to facilitate commitment if a patient becomes violent or the family is on the verge of collapse.
- Don't feel guilty and don't make the patient feel guilty. Bipolar disorder results from an imbalance of chemicals in the brain and not from anyone's fault.

Support for the Family. Unfortunately, actions that support a bipolar disorder patient may not be intuitive, and they take their toll. Loved ones must also care for themselves or they may follow a path to severe depression themselves. They should try any and all methods to boost energy and reduce stress, such as the following:

- Exercise.
- Meditation.
- Relaxation techniques.
- Holidays away from the patient.
- Involvement in hobbies.
- Involvement in support groups, Internet resources with chat rooms, and message boards for bipolar disorder caregivers can be very helpful.

Interpersonal and Social Rhythm Therapy

Interpersonal problems (e.g., family disputes) and disruptions in daily routines or social rhythms (e.g., loss of sleep or changes in meal times) may make people with bipolar disorder more susceptible to new episodes of their illness. A form of psychosocial treatment called interpersonal and social rhythm therapy (IPSRT) focuses on minimizing these potential triggers. Preliminary evidence suggests that IPSRT, in combination with drug therapy, can help dampen depressive symptoms and is superior to drug therapy alone.

Lifestyle Factors

Exercise. Exercise is an important part of treatment, particularly in order to help manage weight gain. It also helps increase feelings of well-being.

Sleep Management. Good sleep hygiene may be of particular importance for bipolar patients. Of particular interest was a study reporting that techniques used to enforce healthy sleep were very effective in reducing

mood cycling. In the study, patients tried to remain inactive in a dark room for 10 to 14 hours each night for three months. [For more information on sleep, see, Insomnia.]

Dietary Factors. A healthy diet low in saturated foods and rich in whole grains, fresh fruits, and vegetables is important for anyone. People with bipolar disorder should be sure to maintain a regular healthy diet. They may need to restrict calories if they are on medications that increase weight.

Some research indicates that consumption of omega-3 polyunsaturated fatty acids found in oily fish, such as mackerel, sardines, salmon, and bluefish, may help reduce the symptoms of a variety of psychiatric illnesses, including bipolar disorder. Studies are under way investigating capsules containing compounds called eicosapentanoic acid (EPA) and docosahexaenoic acid (DHA) in patients who have not responded to other agents. A preliminary 2002 study found that they may benefit patients with depressive symptoms more than those with mania.

Also under investigation is a member of the vitamin B complex, inositol, which may have a positive effect on depression.

WHERE ELSE CAN HELP BE OBTAINED FOR BIPOLAR DISORDER?

National Depressive and Manic-Depressive Association (www.bipolarnetwork.org ▶▶). Call (310-794-9913).

The Stanley Bipolar Treatment Network (www.bipolarnetwork.org ▶▶). Call (800-518-7326).

Child & Adolescent Bipolar Foundation (www.bpkids.org ▶▶). Call (847-256-8525).

Depression and Related Disorders Association (www.med.jhu.edu/drada ▶▶). Call (410-955-4647).

National Foundation for Depressive Illness (www.depression.org). Call (800-239-1265).

Lithium Information Center (www.miminc.org/aboutlithinfoctr.html). Call (608- 827-2470).

National Institute of Mental Health (www.nimh.nih.gov ▶▶). Call (800-421-4211).

National Alliance for the Mentally Ill (www.nami.org). Call (703-524-7600) or the NAMI HelpLine at (800-950-6264).

National Mental Health Association (www.nmha.org ▶▶). Call (703-684-7722) or the Mental Health Information Line at (800-969-6642).

American Institute for Cognitive Therapy (www.cognitivetherapynyc.com). Call (212-308-2440).

Association for the Advancement of Behavior Therapy (www.aabt.org). ▶▶ Call (800-685-AABT).

The American Psychiatric Association (www.psych.org). Call (202-682-6000).

The American Psychological Association (www.psychologicalscience.org). Call (202-783-2077).

The American Psychiatric Nurses Association (www.apna.org). Call (703-243-2443).

American Academy of Child and Adolescent Psychiatry (www.aacap.org). Call (202-966-7300).

Expert Knowledge Systems (www.psychguides.com ▶▶).

Mental Health Net (<http://mentalhelp.net> ▶▶).

Internet Mental Health (www.mentalhealth.com) is a free encyclopedia of mental health information.

Find a therapist at (www.1-800-therapist.com).

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