

## The Treatment of Bipolar Disorder

**B**ipolar affective disorder, commonly called manic-depression, affects approximately 1 percent of the United States' population (3 million individuals.) It is a mood disorder classified by one or more manic episodes, interspersed with one or more depressive episodes. Although bipolar disorder can become disabling, it is among the most treatable of the psychiatric illnesses.

### Course of Illness

The onset of bipolar disorder can occur at almost any age—from adolescence to the later years—with the majority affected before the age of 30. Studies have shown that between 30 and 35 percent of bipolar patients experience the onset of the illness between 20 and 30 years of age. Nearly 25 percent experience the onset between the ages of 40 and 50.

Another study, in looking at the lifetime prevalence and age onset of *major depression* and *bipolar disorder* from ten countries, found some *differences* between the two disorders. In major depression, the lifetime rates varied widely across countries, while the rates of bipolar disorder were more consistent.

Another difference between the two disorders was the preponderance of females in the rates of major depression, while in bipolar disorder there was not preponderance of the disorder in either sex.

Overall, the study revealed that persons with bipolar disorder and major depression, compared to persons with no psychiatric disorder, are at greater risk for substance abuse, suicidality, emergency room and medication use for emotional problems, and impairment in work and marriage. This risk was found to be generally higher in persons with bipolar disorder as opposed to major depression.

### Causes of Bipolar Disorder

Many studies into the roots of bipolar disorder have centered on genetic research. Close relatives of people suffering from bipolar illness are 10 to 20 times more likely to develop either depression or manic-depressive illness than the general population. In fact, about two-thirds of people suffering from manic-depressive

### SYMPTOMS OF BIPOLAR DISORDER

#### A Manic Episode

A manic episode is characterized by a distinct period of a mood change that is either elevated (to the point of elation), expansive, or irritable. During this phase, which may last from several days through a few months, the patient's behavior causes difficulties in both professional and social activities.

#### Symptoms of the *manic phase* may include:

- ❖ decreased need for sleep
- ❖ increased pressure of speech
- ❖ distractibility
- ❖ inflated self esteem or grandiosity
- ❖ excessive involvement in activities that have a high risk for pain consequences that are not recognized.

The patient may become psychotic with delusions and hallucinations. Frequently, those experiencing a manic episode do not realize they are affected and will, therefore, resist any medical treatment attempt. Close friends will recognize the mood and behavior patterns as being excessive, while the casual observer may not see anything disturbing.

#### A Depressive Episode

A depressive episode usually lasts two weeks to many months, during which time the patient will experience a lack of interest or pleasure in all activities. Patients may describe themselves as feeling sad or blue, devoid of motivation, or worthless. These feelings and thoughts may or may not be stated openly in front of others.

#### Symptoms of the *depressive phase* may include:

- ❖ sleep disturbance (sleeping more or less than usual)
- ❖ changes in appetite
- ❖ feeling sad, worthless, or guilty without cause
- ❖ concentration difficulties
- ❖ thoughts of death and/or suicide attempts

The course of a depressive episode may vary from person to person. Symptoms may develop over a period of days or weeks, or they may occur suddenly, without warning. Sudden onset of this condition can be caused by external factors, including stress, death of a family member, or divorce. Duration of an episode will vary and depends on medical treatment employed.

disorder have relatives who suffer from some form of depression. If one parent suffers from manic-depressive illness, a child has a 12-15 percent risk of suffering from a depressive disorder; if both parents suffer from manic-depressive illness, the children have at least a 25 percent chance of developing a depressive disorder or manic-depressive disorder and a much higher chance of suffering some type of behavioral disorder.

Several studies suggest that imbalances in the biochemistry controlling a person's mood could contribute to manic-depressive illness. For example, people suffering from either manic-depressive disorder or major depression often respond to certain hormones (TRH) or steroids (dexamethasone) in a way that indicates they have biological abnormalities associated with their mood dysfunction. Considerable research points to the possibility that bipolar patients' neurotransmitters (chemicals by which brain cells communicate) become imbalanced during various phases of the disease. Also, people suffering from depressive illness have sleep patterns in which the dream phase begins earlier in the night than normal. These studies indicate that manic-depressive illness and major depression may be caused by biochemical imbalances.

### *Treatment of Manic Episode*

Medical treatment usually begins with lithium, which is associated with a positive reduction of manic symptoms. Acting as a mood stabilizing agent, without the properties of a sedative or tranquilizer, lithium gradually alleviates manic symptoms over a period of seven to twelve days. Twenty percent of those who use lithium become completely free of symptoms. Those who respond best to lithium are patients who have a family history of depressive illness and who have periods of relatively normal moods between their manic and depressive phases.

Lithium's side effects include tremor, excessive thirst, frequent urination and upset stomach. Hypothyroidism occurs in approximately ten to fifteen percent of treated patients, and can be treated with thyroid supplementation. There is also a slight risk of bradycardia (slow heart rate) in people with pre-existing heart conditions or the elderly. At therapeutic doses, lithium is generally very safe, however, lithium toxicity, which usually results from overdose or changes in kidney function, is a serious and poten-

tially fatal condition. As a result, lithium levels and kidney function need to be monitored regularly.

If a patient is either unable to take lithium or not responding to it, an alternative anticonvulsant drug such as carbamazepine (Tegretol), or valproate (Depakote) may be prescribed. Early in treatment, an antipsychotic agent (i.e., a major tranquilizer or neuroleptic such as Haloperidol) or a high potency benzodiazepine (i.e., a minor tranquilizer such as Clonazepam) may be prescribed in order to control agitation. These medications are usually tapered off when the agitation subsides.

If a patient experiencing a severe manic episode does not respond to drug therapy, or if a patient is at high risk for suicide, lithium may be discontinued and electroconvulsive therapy (ECT) may be prescribed. Two major studies have found ECT to be a valuable alternative to medications in treating acute mania.

### *Treatment of Depressive Episode*

Bipolar depression generally is treated according to a "drug decision tree." That is, medical treatment usually is begun with one method, which includes a sequence of different drugs added to and subtracted from the therapy based upon contraindications and effectiveness.

Usually, a depressive episode in bipolar patients is first treated by optimizing the lithium dose. Often, however, breakthrough depressive symptoms appear, and an antidepressant or a mood stabilizer will be added to the medical treatment regimen. Four classes of antidepressants that may be considered for this treatment are TCAs, MAOIs, SSRIs and SNRIs (see descriptions on next page.)

### *Theories on How Lithium Works*

Lithium is proposed to work by bringing various neurotransmitter systems in the brain into balance. Scientists believe lithium may affect the impact neurotransmitters have on the brain cells, thus altering moods. However, the specific biological basis for the clinical efficacy of lithium is unknown. Lithium paradoxically relieves and prevents both mania and depression, states that appear to be opposites (although it is not particularly efficacious in the treatment of acute depression.) Unlike many psy-

▲ **TCAs** - Although tricyclic antidepressants have proven effective in the medical treatment of major depression, their relative efficacy and ability to precipitate mania or rapid-cycling in bipolar depressive patients have not been well explored.

▲ **MAOIs** - Research indicates that monoamine oxidase inhibitors may be more effective in the medical treatment of bipolar depression than TCAs. However, patient compliance may be a problem with this class of drugs due to side effects and dietary restrictions. Moreover, like TCAs, MAOIs may precipitate the onset of mania or mild manic states. Unfortunately, most studies with MAOIs have not included patients with bipolar depression and, therefore, further research is needed for their use.

▲ **SSRIs** - Selective serotonin reuptake inhibitors, which include agents such as paroxetine (Paxil), fluoxetine (Prozac), and sertraline (Zoloft), are more easily tolerated than many of the tricyclic antidepressants in the medical treatment of depression due to their favorable side-effect profiles.

It is unclear whether the SSRIs may be less likely to induce mania in patients, compared to TCAs and MAOIs. The SSRIs are widely used, but because of their relatively recent introduction, few studies are available on their use in bipolar patients.

▲ **SNRI** - Venlafaxine (Effexor) is a serotonin nonselective reuptake inhibitor. Effexor is highly effective in treatment of refractory unipolar depressed patients and further studies are warranted with bipolar patients. This drug has a benign side effects profile like the SSRIs and also affects norepinephrine in addition to serotonin.

Bupropion (Wellbutrin) is an antidepressant that predominately affects dopamine and is well tolerated and widely used in unipolar and bipolar depressed patients. Some evidence suggests that it is less likely to induce mania than other antidepressants, but more systematic clinical trials are needed to accurately assess this possibility.

chotropic drugs, which have clear effects at one or a few sites involved in the regulation of neurotransmitters, lithium's actions in these systems are diverse.

Current research into lithium's mechanism of action are focusing on "second messenger systems." These systems (which include adenylate cyclase activity and the phosphatidylinositol cascade) mediate the effects of neurochemicals on nerve cells, thereby playing an important role in regulating the flow of

nerve impulses. Other theories surrounding lithium's mechanism of action have evolved from the effects of lithium on ion transport, neurotransmitter release and receptor function.

### *Treatment-Resistant Bipolar Disorder*

Two forms of bipolar disorder that tend not to respond to lithium are "rapid-cyclers" and those with "mixed forms." Rapid-cycling consists of at least four episodes of the illness, either mania or depression in a year, but most rapid-cycling patients have more than four episodes. Patients with mixed forms have mania that is dysphoric rather than euphoric in mood. Studies suggest 40% of bipolar patients have mixed moods and about 10% have rapid-cycling.

There have been some new developments in successfully treating rapid-cycling forms of the illness. The anticonvulsant drugs, Tegretol and Depakote, are showing promise in treating these treatment-resistant forms of bipolar disorder.

One theory surrounding patients with rapid-cycling disorder is that their thyroid function is being disturbed in some subtle way, and adjunctive treatment with thyroid hormones is often helpful in patients with the difficult to treat illness. Drugs used to treat heart problems, such as calcium channel blockers, have been proposed as being effective but still need to be further studied. These compounds are used in the more serious resistant forms of the illness. Clozapine (Clozaril) has also appeared to have positive effects in some treatment-resistant rapid-cycling patients.

There are also several new compounds in the early stages of development for treatment-resistant bipolar disorder, but research has yet to show whether they are safe in humans. Several European drugs with novel activities, including those that enhance serotonin uptake, inhibit dopamine uptake, and are agonists for alpha receptors, show hints of success for bipolar disorder.

## *Basis of Treatment-Resistance*

There are a number of hypotheses of why bipolar illness seems to be more difficult to treat than was initially thought. One theory providing some answers for treatment resistance is the “kindling model.” This representative model explains how acute events in the environment could have long-lasting effects on brain chemistry and microstructure. The kindling model proposes that repeated environmental stimuli leads to progressively greater neural responses which change brain excitability and behavioral responsiveness in a long-lasting fashion.

The kindling model theorizes that acute psychosocial stresses (such as separations and losses) affect gene expression. Typically, the first episodes of bipolar disorder are provoked by life events. Later on, the bipolar episodes seem to take on a life of their own and one episode will kindle another, even in the absence of psychological stress. This implies that if enough stressor-related episodes occur, cycles of affective illness may also begin to occur automatically; that is, without psychosocial stresses.

This theoretical perspective supplements a large amount of existing clinical data emphasizing the importance of early intervention and sustained long-term preventative (prophylactic) treatment. In this fashion, not only would severe episodes be prevent-

ed, but their sensitizing effect in making a patient more vulnerable to further recurrences would be prevented as well. Once a patient is successfully treated, they should consider staying on this effective regimen indefinitely since discontinuation of lithium (or other agents) is associated with a very high relapse rate and in a small number of instances, patients do not respond again when they are placed back on their previously effective drug.

## *Integration of Psychotherapy Into Treatment*

The need for integrating psychotherapy and pharmacologic therapy is made evident with the fact that after three years of drug therapy, only about 40 percent of patients usually remain well. Recent studies have found that the combination of psychotherapy and pharmacology seem to reduce relapses for bipolar disorder patients. Patients who engage in psychotherapy are more likely to adhere to drug regimens, are less likely to deny their illness, suffer less trauma from having bipolar disorder and show improved social and occupational functioning.

Several studies suggest that bipolar patients who return from the hospital to stressful home environments are at risk for relapse following hospitalization. It is recommended that family counseling be implemented so that the risk of a relapse for the patient is decreased.

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