Diagnosing and treating bipolar disorder offers an array of challenges to the clinician. It is a multidimensional syndrome that can have numerous clinical presentations with a variety of symptom domains in the same individual. It can be difficult to diagnose and evidence shows that it can often be misdiagnosed. With that challenge, it is important to review the various aspects of bipolar disorder and the approaches to treatment, old and new. A review of the latest scientific data can guide us to make informed clinical decisions to make a difference in the quality of care for our bipolar patients. (Adv Stud Med. 2004;4(10D):S881-S891)

Bipolar disorder, possibly more than any of the other syndromes in psychiatry, is in the process of evolution and re-evaluation. Although the disorder was previously thought to afflict approximately 1% of the population, more recent epidemiologic studies indicate that it is much more prevalent; some studies suggest that 5% or more of the population may suffer from the disorder. This marked increase in prevalence estimates is primarily because of the inclusion of individuals who have milder but still clinically relevant and often disabling forms of the disorder. Furthermore, there is increasing recognition and emphasis on the treatment of the depressed phase of the disorder. The depressed phase of the illness is manifested more frequently, carries high morbidity and mortality, and is often difficult to treat effectively.

In addition to the evolution in conceptualization and diagnosis of the disorder, treatment options are expanding rapidly. Until recently, lithium and valproate were the only agents the Food and Drug Administration (FDA) approved for the treatment of the disorder. With increasing recognition of the clinical importance of the disorder, research into the clinical management of the many expressions of the bipolar syndrome has increased dramatically. This, in turn, has resulted in a greatly improved understanding of the neurobiology of the disorder and an increased number of new agents available for effective intervention. As these treatments evolve, we are increasingly able to target treatments specific to an individual and illness phase, thus maximizing treatment effectiveness while minimizing the side-effect burden.

Prevalence of the Disorder

Until recently, it was generally thought that approximately 1% of the population suffered from bipolar disorder. However, these estimates were based primarily on patients with bipolar I syndrome. It is becoming increasingly clear that a larger percentage of the population suffer from the varying forms of the disorder. The increase in rates found in many of the more recent studies can be attributed to the increased diagnosis of bipolar type II patients and the inclusion...
of “softer” clinical manifestations of the disorder. Although 4 days is the minimum requirement for the diagnosis of a hypomanic episode in the Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition (DSM-IV), patients frequently experience episodes lasting 1 to 3 days. Antidepressant-induced mania, sometimes referred to as “bipolar III,” may also indicate the presence of an underlying bipolar disorder.

Several studies have found a high rate of bipolarity in patients presenting with depression. Akiskal et al noted that 30% to 55% of a cohort of patients with major depression suffered from some form of bipolar disorder if softer and subthreshold forms of the illness were included. In a prospective study of 108 consecutive patients with anxiety and depressive symptoms in a family practice setting, the rate of bipolar spectrum disorders including types I, II, III, and cyclothymia was 25.9%. The bipolar diagnosis was frequently not recognized at the time of initial treatment. In an Italian study of depressed outpatients in a private practice setting, the rate of bipolar I was found to be 49% and the rate of bipolar II was noted to be 45%. A French multicenter study conducted by Hantouche et al was designed to test the feasibility of validating the diagnosis of soft bipolar spectrum by practicing clinicians. Of the 537 patients with major depressive disorder, the rate of bipolar type II disorder was found to be 22% at initial evaluation. After training and more systematic evaluation, the rate was found to nearly double to 40%. Therefore, increasing clinician awareness and sensitivity to the signs of the disorder resulted in much higher diagnostic rates. In a study by Angst and Presig, after the onset of illness, bipolar patients spent approximately 19% of their lives in mood episodes, and the naturalistic follow-up study by Goldberg et al found that only 41% of bipolar patients had a good overall outcome over 4.5 years.

**PSYCHOSOCIAL ISSUES**

Patients with bipolar disorder are at much higher risk for interpersonal and psychosocial difficulties. Many patients with bipolar disorder experience a broad variety of psychosocial difficulties. Calabrese et al assessed the functional status of 3059 individuals in the community with bipolar I or II disorder. Approximately 50% of the bipolar sample reported experiencing serious problems at work compared to 25% of the controls. Approximately 25% of the bipolar cohort had been arrested, jailed, or convicted of a crime more serious than driving while intoxicated compared to only 5% of controls. Individuals with bipolar disorder also experienced difficulties in social and family interactions. Women tended to have more problems with social and family life, whereas men had more difficulty with legal issues. Altshuler et al found that the Global Assessment of Functioning scale correlated negatively with the Hamilton Rating Scale for Depression (HAM-D), even though none of the patients had HAM-D scores high enough to diagnose a clinical depression. Therefore, even subsyndromal depressive symptoms resulted in increased overall functional impairment.

**GENETIC FACTORS**

Although bipolar disorder is one of the most heritable of the psychiatric disorders, identifying the specific genes involved in the disorder remains difficult. Bipolar disorder appears to be oligogenic (ie, multiple susceptibility genes each contribute a small effect to the expression of the syndrome). The genes responsible for the disorder are probably common in the general population and it is only when specific combinations of these genetic elements are present that the syndrome is manifested. Therefore, separation of the genetic combinations from normal controls may be difficult as the genetic contributions overlap. Furthermore, differing genetic patterns may result in similar phenotypic expressions of the disorder, making generalization of results difficult.

Pharmacogenetics, or the determination of genetic markers in patients responding to a particular medication, is a promising approach to developing individually targeted psychopharmacologic interventions. For example, it has been observed clinically that lithium responders have distinct clinical characteristics. By analyzing genetic markers in lithium responders, specific genetic loci have been identified. In this manner a distinct clinical, biological, and genetic profile of the responders may be identified.

**DSM-IV DIAGNOSTIC CRITERIA**

The criteria for a manic episode as outlined in the DSM-IV require the presence of a period of elevated, expansive, or irritable mood lasting at least 1 week.
The duration may be briefer if a hospitalization is required. Three or more associated symptoms must be present (4 or more if the mood is only irritable), including inflated self-esteem or grandiosity, decreased need for sleep, increased verbalization or pressure of speech, insomnia or hypersomnia, psychomotor agitation or retardation, flight of ideas, distractibility, increased goal-directed activity, and excessive involvement in pleasurable activities with a high potential for painful consequences. At least 1 manic episode must be present for a diagnosis of bipolar I disorder.

A diagnosis of bipolar II disorder requires the presence of at least 1 or more episodes of major depression and at least 1 hypomanic episode. A hypomanic episode consists of a distinct period of elevated, expansive, or irritable mood lasting at least 4 days. At least 3 associated symptoms must be present (4 if the mood is irritable). The associated symptoms are similar to those listed for manic episode, although only 7 associated symptoms are listed instead of the 9 listed for manic criteria.

Cyclothymic disorder is characterized by at least 2 years of brief periods of mild depression and hypomania, lasting a few days to a few weeks. One year is required for children or adolescents. There must be no period of euthymia lasting more than 2 months. During the first 2 years of the disorder, the individual must not have experienced a manic, mixed, or major depressive episode.

**Delays to Diagnosis**

Despite the greater attention recently given to the disorder, problems with delay in diagnosis and misdiagnosis are still very common. Hirschfeld et al surveyed 600 members of the National Depressive and Manic Depressive Association (now the Depression and Bipolar Support Alliance [DBSA]) with bipolar disorder for their experience with the mental health system. More than 33% of the group sought help within 1 year after symptom onset. However, 69% indicated that they were misdiagnosed, most frequently with major depressive disorder. Those patients who were initially misdiagnosed saw an average of 4 physicians before the correct diagnosis was made. The correct diagnosis was not made for more than 10 years in more than 33% of the sample. The rate of accurate diagnosis was better than that noted in a 1994 survey in the same group. In that study, 73% of patients noted that they had been misdiagnosed initially. Even when a previous manic or hypomanic episode occurred, there was still a high rate of misdiagnosis.

**Increasing Diagnostic Accuracy**

The varied presentation and expression of the bipolar syndromes make for diagnostic confusion, misinterpretation of symptoms, and delay of treatment. There are several aspects of symptom expression that make for problems in accurate diagnosis, including the intermittent expression of symptoms, frequent absence of classic manic symptoms, late presentation of mania, and difficulties in obtaining accurate history among others (Table 1).

Alternatively, there are several aspects of the presentation of the bipolar patient that should raise the clinician’s suspicions to the presence of the syndrome, even in the absence of the clear or full expression of the disorder (Table 2). For example, anger or irritability, even in the absence of significant depressive symptoms, may indicate the presence of bipolar disorder. Benazzi noted that patients with depression expressing angry affect were more comparable to bipolar patients as compared to those patients without anger. The age of onset of depression was lower in patients with anger. Other indicators of the presence of a bipolar syndrome include positive family histories ofmania, antidepressant-induced manic symptoms, increased mood lability, more motor retardation, a greater frequency of depressive episodes, a more severe course of illness, and a more

---

**Table 1. Causes of Delays in Diagnosis of Bipolar Disorder**

- Intermittent expression of symptoms
- Frequent absence of classic manic symptoms
- Presence of subsyndromal symptoms
- Difficulty obtaining history owing to poor insight or lack of recall of previous episodes
- Presentation of mania late in the course of illness
- Overlap with other syndromes (eg, borderline personality disorder, impulse disorders, ADHD)
- Variable psychotic phenomena, including mood incongruent phenomena
- Substance abuse may mimic or obscure symptoms

ADHD = attention-deficit hyperactivity disorder.
acute onset and offset of affective symptoms. Temperamental “character traits” or periods of high energy, even if brief, may also be clues to the diagnosis. Bipolar patients frequently also manifest impulse problems, promiscuity, and aggressive behavior. Because many of the traits in bipolar patients may be adaptive or positive, they may not be viewed as clinically significant. For example, a successful hard-driving executive who has “boundless” energy and requires little sleep may be seen as well suited to his/her position rather than an individual requiring clinical attention. Alternatively, an outgoing and engaging individual is often viewed as very well adapted socially and may be envied for his/her social skills and capacities. However, on careful history taking, there is often evidence of other symptoms typical of mania or depression.

COMORBIDITY

Comorbidity is common in bipolar disorder. In a study of 288 outpatients with bipolar I or II disorder, 65% met criteria for a lifetime history of another disorder. Anxiety disorders were reported in 42%, whereas the rate of comorbid eating disorders was 5%. A history of substance abuse was found in 42% of the sample. The rate of comorbidity was similar among patients with bipolar I and II. Comorbid anxiety has been associated with early onset, more rapid cycling, increase in course severity, poor response to treatment, and poor outcome. Psychiatric comorbidity has been noted to be higher in patients with bipolar II compared to patients with bipolar I in some studies, but not in others.

A high rate of substance abuse has been consistently noted in patients with bipolar disorder and is higher than the rate observed in most other axis I disorders. In a study by Chengappa et al, 57.8% of patients with bipolar I were found to abuse drugs and alcohol. In patients with bipolar II, the rate was found to be 39%. In a retrospective study of 267 outpatients with bipolar disorder, the lifetime rate of alcoholism was noted to be higher in men (49%) than women (29%). Compared to the general population, the increased risk rate was much higher in women (odds ratio = 7.35) compared to the increase in men (odds ratio = 2.77). The presence of comorbid substance abuse significantly worsens the prognosis. Worsened outcome among substance abusers may be related to increased problems with compliance, increased denial, problems differentiating symptoms in the presence of substance abuse, and other factors.

The rate of comorbid personality disorders also tends to be high in bipolar disorder. In a study of remitted bipolar patients, 28.8% were found to have comorbid personality disorders, primarily of the cluster B and cluster C subtypes. Many of the symptoms of borderline personality disorder overlap with those symptoms found in bipolar patients, and a significant proportion of patients with borderline personality actually may be suffering from bipolar syndrome. In one study, 44% of patients diagnosed with borderline personality disorder were thought to have bipolar disorder. If patients with antidepressant-induced switching to mania were included, the rate increased to 69%.

MANIA

Acute mania is the most dramatic phase of the bipolar syndrome and requires rapid and effective treatment to avoid multiple untoward consequences. Bipolar disorder accounts for 1 in 7 psychiatric emergencies. In cases of extreme agitation or threatening behavior, intramuscular (IM) injections of medications may be required. Until recently, the most commonly used combination of agents was IM haloperidol and lorazepam. Although this combination was effec-

Table 2. Diagnostic Clues to the Bipolar Disorder Syndrome

<table>
<thead>
<tr>
<th>Clues to the Bipolar Disorder Syndrome</th>
</tr>
</thead>
<tbody>
<tr>
<td>Presence of angry affect or irritability, even in the absence of other affective symptoms</td>
</tr>
<tr>
<td>Poor response to antidepressants</td>
</tr>
<tr>
<td>Promiscuity or impulsive tendencies</td>
</tr>
<tr>
<td>Aggressive behaviors, especially if impulsive</td>
</tr>
<tr>
<td>History of childhood ADHD, especially with poor response to stimulants</td>
</tr>
<tr>
<td>Childhood behavioral problems</td>
</tr>
<tr>
<td>Family history of bipolar disorder</td>
</tr>
<tr>
<td>Childhood onset of depression</td>
</tr>
<tr>
<td>Acute onset and offset of depression</td>
</tr>
</tbody>
</table>

ADHD = attention-deficit hyperactivity disorder.
tive in controlling acute symptoms, significant side effects such as acute extrapyramidal symptoms, including dystonia, and excess sedation often occurred. IM atypical antipsychotic formulations are now available. Ziprasidone is available in an IM formulation and has been noted to be effective within 15 to 30 minutes with minimal motor side effects or sedation.33 Olanzapine has also been found to be effective in IM formulation and has been shown to be equivalent to haloperidol in effectiveness.34

**MIXED EPISODES**

Increased attention is appropriately being given to mixed manic episodes. Mixed episodes were first described by Kraepelin and are characterized by the presence of depressive and manic symptoms during the index episode.48 They may represent a more virulent form of the illness and have been associated with increased suicidal ideation, refractoriness to treatment, and a poor response to lithium.49 In a survey of 184 adult inpatients, 58% of patients with mixed mania were suicidal compared to only 1.3% of patients with pure mania.50 Suicide attempts before the index episode were also increased in those patients with mixed episodes (37% vs 8%). The probability of achieving remission declined by 49% for each prior suicide attempt.

**DEPRESSION**

Although the manic episodes associated with bipolar disorder tend to be the more dramatic element of the disorder, it is the depressed phase that predominates in most patients and is often the most difficult to treat. In a 13-year prospective study of 146 bipolar I patients, it was found that patients reported depressed mood 32% of the time, manic/hypomanic symptoms 9% of the time, and mixed symptoms 6% of the time.51 In a 15-year follow-up study, it was found that depressive episodes of illness in patients with bipolar I lasted significantly longer than manic episodes.52 Morbidity was higher during the entire follow-up period in patients who initially presented with a depressed episode.

**PSYCHOTIC FEATURES**

Although psychosis is commonly observed in the bipolar syndrome, it has received much less systematic study than the affective elements of the disorder. In a study of 179 patients hospitalized with a manic episode, individuals with psychotic features had greater overall impairment as measured on the Global Assessment Scale.49 However, the severity of mania scores did not differ between the psychotic and nonpsychotic cohorts. Treatments that successfully treated mania also decreased psychosis severity scores. Coryell et al found that psychotic features were associated with a greater amount of time ill during the 5-year follow-up period.43 However, the time to initial recovery and time to first relapse was not different between the psychotic and nonpsychotic cohorts. Response to acute lithium treatment was also similar between the 2 groups. Keck et al did not note any difference between psychotic and nonpsychotic bipolar I cohorts and did not find any distinguishing demographic, psychosocial, or vocational variables.42 A family history of bipolar disorder was significantly more common in patients with nonpsychotic forms of the disorder. The presence of psychosis, whether it was mood congruent, surprisingly did not result in a worse overall outcome in this study. In a study of 50 patients with bipolar disorder followed for 8 months after their first hospitalization for a manic episode, mood-incongruent psychotic features were found to result in more weeks with psychosis compared to patients with mood-congruent psychosis.43 The mood-incongruent group had poorer overall functioning during follow-up.

**SUICIDE RISK**

Suicide rates are high in bipolar disorder and early onset of the disorder is associated with increased suicide rates.44 It has been estimated that at least 25% to 50% of all patients with bipolar disorder attempt suicide at least once.45 Suicide rates among patients with bipolar disorder average 0.4% per year, which is more than 20 times higher than in the general population.46 In a Swedish study of 15 386 hospitalized patients with bipolar disorder, the standardized mortality ratios for suicide was 15.0 for males and 22.4 for females.50 This compared to rates in unipolar depression of 20.9 and 27.0, respectively.

Treatment with lithium has been shown to decrease suicide rates dramatically. In a study of pooled data from 34 studies of 16 221 patients, the risk for all suicidal acts per 100 person-years was 3.10 without lithium.49 This rate dropped dramatically to 0.210 during treatment compared to the 0.315 baseline rate for the
general population. In one study, the risk of suicide was higher during treatment with divalproex compared to lithium. The risk of death was 2.7 times higher with divalproex.

Some of the risk factors for suicide among patients with bipolar disorder are acute depression, especially when there is hopelessness, turmoil, global insomnia, anhedonia, and anxiety or panic; mixed episodes and cycling within an episode; substance abuse; aggression/impulsivity; history of suicide attempts (personal or familial); and early onset of the disorder.

**MEASURING OUTCOMES**

There are several rating scales that are used for the assessment of symptom severity in patients with bipolar disorder. The Young Mania Rating Scale (YMRS) is one of the most widely used in research for the manic phase of the illness. The YMRS consists of 11 clinician-rated questions. Rated items include elevated mood, motor activity, sexual interest, sleep, irritability, speech rate and amount, language-thought disorder, thought content, disruptive-aggressive behavior, appearance, and insight. Alternately, the Mania Rating Scale has been used in recent studies. This is based on an 11-item scale derived from the Schedule for Affective Disorders and Schizophrenia, Change Version; total score measures severity of manic symptoms.

There are several rating scales for the measurement of depression symptom severity. The HAM-D in a 21- and 17-item format are the most commonly used. This is a clinician-rated scale to assess the presence and magnitude of depressed mood, guilty feelings, suicidality, sleep difficulties, anxiety, and weight loss among others. The Montgomery-Asberg Depression Rating Scale is also widely used and assesses for treatment changes in the severity of a variety of symptoms, including depressed mood, sleep, appetite, energy, concentration, and suicidality.

The Positive and Negative Syndrome Scale is one of the most widely used scales for dimensions associated with schizophrenia and other psychotic disorders. There are 30 clinician-rated questions that assess the extent of positive symptoms, such as delusions, hallucinations, and thought disorganization; negative symptoms include items such as blunted affect, emotional withdrawal, poor rapport, and social withdrawal, in addition to general psychopathology.

**SCREENING FOR BIPOLAR DISORDER**

To improve the diagnosis of bipolar disorder, Hirschfeld et al developed the Mood Disorder Questionnaire (MDQ). This screening instrument includes 13 yes/no questions concerning manic or hypomanic symptoms. The respondent is also queried as to the presence of multiple simultaneous symptoms and the psychosocial problems that they may have caused. The screen is considered positive if multiple symptoms are present at the same time and they are of at least moderate severity. The MDQ has been translated in several languages and is available online through the DBSA Web site at http://www.dbsalliance.org/questionnaire/screening.asp.

In a nationwide survey of 85,000 adults using the MDQ, the lifetime prevalence of bipolar disorder I and II was found to be 3% (4% after nonresponse bias included). The highest prevalence rate was in the 18- to 24-year age group at 9%. The high rate in this age group is considered to be partially an artifact; however, it highlights the tendency for early onset of the disorder. Thirty-three percent of the sample reported experiencing difficulties before age 15 years, and 27% reported the onset of difficulties between ages 15 years and 19 years. Only 20% of patients with positive screens indicated that they had previously received a diagnosis of bipolar disorder by a physician and 33% had been diagnosed with unipolar disorder.

Life charting has also been shown to be an effective means of detecting and tracking periods of mood instability and response to treatment. Life charting can help clinicians monitor the episodic course of the illness and the treatment response to often complicated medication regimens. It may aid patients and families to identify early signs of decompensation and to gain insight into the course of the disorder. Manuals and forms for clinicians and patients are available at http://www.bipolarnews.org/Clinician%20Life%20Charting.htm.

**PSYCHOPHARMACOLOGIC ADVANCES**

After the introduction of lithium in the early 1950s, there were few advances in the treatment of bipolar disorder for several decades. Although lithium was clearly efficacious, the medication appeared to work well primarily in a particular subgroup of patients. A good response to lithium has been associ-
ated with an episodic course interspersed by euthymic periods, 4 or less cycles per year, and a family history of bipolar disorder. Alternatively, a poor lithium response may be predicted by early onset, rapid cycling (more than 4 episodes per year), a chronic course, mixed episodes, and a history of substance abuse.63,64

The anticonvulsant carbamazepine was subsequently also found to be effective in mood stabilization65 and appeared to be efficacious in a different subpopulation of patients compared to lithium.66 Valproate was also found to be effective in stabilizing mood and offered a differential treatment response compared to lithium.64 In a study by Bowden et al, divalproex and lithium were found to be significantly more effective compared to placebo in reducing the symptoms of acute mania.67 The efficacy of divalproex was determined to be independent of prior responsiveness to lithium.

There are several new antiepileptic agents that are increasingly being used in the treatment of acute mania. Lamotrigine is effective for the prevention of manic and depressive episodes.68,69 Lamotrigine is particularly effective in the treatment of bipolar depression, but was not effective in the treatment of acute mania in 3 studies. However, the titration schedule must be kept slow to minimize the risk of potentially serious Stevens-Johnson syndrome, especially if used concurrently with valproate.70 Oxcarbazepine possesses a chemical structure similar to carbamazepine,71 but its efficacy in bipolar disorder has not been established. The side effects are less serious than those side effects observed with carbamazepine.72 Topiramate also may be a useful adjunctive agent, but double-blind, placebo-controlled studies failed to demonstrate efficacy in acute mania.73,74 Topiramate, in contrast to many of the other mood-stabilizing and antipsychotic drugs, has the advantage of inducing weight loss in some individuals. It has been used as an adjunctive agent to offset the weight-enhancing effects of medications, such as olanzapine.75

**ATYPICAL ANTIPSYCHOTICS IN BIPOLAR DISORDER**

The atypical antipsychotic agents are playing an increasing role in the acute and long-term treatment of bipolar disorder. In contrast to the typical antipsychotics that bind to dopamine D2 receptors at greater than 90%, the atypical agents all possess a greater affinity for the 5-HT2A receptor than the dopamine D2 receptor and occupy the dopamine D2 receptor at 70% or less. Each of the atypical agents also possesses a unique pharmacologic profile that is associated with varying clinical actions and side-effect profiles. These distinctions allow the clinician to tailor treatment to the specific individual.

Olanzapine was the first of the atypical antipsychotics approved for the treatment of bipolar disorder. It has been shown to be effective in several studies, alone and in combination with other mood stabilizers.67 Clozapine, the first of the atypical agents available, also has been shown to be effective. Similar to its role in schizophrenia,8 clozapine has been shown to be effective in treatment-resistant bipolar disorder.79 However, its side-effect burden, including the risk of agranulocytosis,80 precludes the use of this agent as first-line therapy.

Of all of the atypical agents, olanzapine and clozapine are the most likely to induce weight gain, hyperlipidemia, and disturbances in glucose metabolism.81 Therefore, caution should be used in administration of these agents in patients already at risk for such problems.82 Obesity in the general population is reaching epidemic proportions and has continued to increase over the past several decades.83 Patients with bipolar disorder or schizophrenia are already at higher risk for health problems and chronic medical illnesses compared to the general population. Medication-induced obesity and the associated metabolic syndrome increase this risk even further. In addition to the health risks, obesity may result in higher noncompliance rates.84

In a study by Zajecka et al, olanzapine monotherapy was compared to treatment with divalproex in hospitalized acutely manic patients.85 No differences were noted in efficacy between the 2 agents. However, patients treated with olanzapine experienced more weight gain and somnolence. The weight gain after 3 weeks on olanzapine was 4.0 kg compared to 2.5 kg on divalproex. There was one death in a patient treated with olanzapine who developed diabetic ketoacidosis. Fontaine et al estimated that the lives saved from suicide prevention with clozapine were nearly offset by the estimated rate of life-years lost through obesity.86 Quetiapine has been shown to be effective as an adjunctive therapy to lithium and divalproex,87 enhancing the clinical effect of both of these agents. In a study of pooled data from several double-blind placebo-controlled studies, quetiapine monotherapy
was shown to be more effective compared to placebo in patients with bipolar I. The average dose of quetiapine was 600 mg/day in this study. Recent studies have shown quetiapine to be effective as monotherapy and adjunctive treatment with mood stabilizers in bipolar mania. Calabrese et al reported that quetiapine was shown to be an effective and well-tolerated treatment for bipolar depression and was not associated with treatment-emergent mania. Although there is some weight gain with quetiapine, it is much more modest compared to clozapine or olanzapine.

Ziprasidone has also recently been approved by the FDA for the treatment of acute mania and mixed episodes. In a 3-week double-blind study, ziprasidone 40 to 80 mg twice daily was more effective in acute mania and mixed episodes (with or without psychosis) compared to placebo on a variety of measures. Separation from placebo was noted on the Mania Rating Scale by the second day of the study and was sustained throughout the length of the study. Patients on ziprasidone did not experience weight gain or clinically significant electrocardiogram changes. Affective symptoms were also improved in a cohort of patients with schizoaffective disorder. In a 52-week, open-label extension of the 3-week study, ziprasidone demonstrated long-term symptom and global improvement in patients with bipolar disorder while displaying a weight- and lipid-neutral profile.

Similar to the other atypical agents, ziprasidone acts as an antagonist of serotonin 2A (5-HT₂A) and D₂ receptors, with greater affinity for 5-HT₂A. Effect on the 5-HT₂C, 5-HT₁D, and 5-HT₁A receptors has been suggested to explain the capacity of ziprasidone to ameliorate negative symptoms and improve cognition. Ziprasidone also inhibits the reuptake of serotonin and norepinephrine, which may underlie antidepressant properties of the agent.

With regard to side effects, ziprasidone treatment is associated with very low rates of weight gain compared to all the other atypical agents other than aripiprazole. Allison et al reported that in at least 81 trials, the greatest weight gain was noted with clozapine (4.45 kg) and olanzapine (4.15 kg). Weight gain on risperidone was intermediate at 4.15 kg and there was negligible weight gain on ziprasidone at 0.04 kg. The data on quetiapine were insufficient and aripiprazole was not included in the analysis.

Risperidone was compared to placebo in a 3-week double-blind placebo-controlled study in acute bipolar mania. A flexible dose of 1 to 6 mg/day was used, with the average dose being 4.1 mg/day. Risperidone was significantly better compared to placebo as early as day 3 and continued throughout the study. Risperidone may result in extrapyramidal symptoms, usually at higher doses. Prolactin increases, menstrual irregularities, and sexual dysfunction may also be observed with this atypical agent. In a study comparing risperidone (1–6 mg/day) to quetiapine (200–1200 mg/day), the rate of sexual dysfunction was 50% in the risperidone cohort compared to 16% in the quetiapine cohort. Prolactin levels were increased in patients treated with risperidone (mean = 57.7 mg/mL) compared to levels in patients receiving quetiapine (13.8 mg/mL). Only 11.7% of patients spontaneously volunteered that sexual dysfunction was present before administration of the questionnaire in the study. Because patients may not make a connection between the onset of the sexual problems and the medications, it is important that these problems be actively elicited by the clinician.

Aripiprazole, the last atypical agent to be introduced, also has been demonstrated to be an effective treatment of acute mania. In a 3-week double-blind study of 262 patients with bipolar disorder manifesting manic or mixed symptoms, 15 to 30 mg per day of aripiprazole was found to be superior to placebo. The response rate on medication was 42% compared to 21% for patients receiving placebo. Aripiprazole has recently received FDA approval for treatment of acute mania.

CONCLUSIONS

Bipolar disorder is one of the most clinically complex syndromes in psychiatry. It is a multidimensional syndrome characterized by mood, behavioral, cognitive, and perceptual symptoms and has a propensity for recurrence in more than 90% of patients. The burden of this disorder causes tremendous individual suffering and societal costs when left untreated or inadequately treated.

The many varying forms of presentations between individuals and within the same patient make accurate diagnosis difficult. The treatment algorithms are also complex because the many different phases of the disorder need to be treated effectively. Despite the many complexities, our understanding of the disorder has been rapidly evolving, as have the range of psychopharmacologic interventions. For many years,
lithium was the only effective treatment available. We now have many new anticonvulsants and atypical agents to help manage this disorder. Targeted use of these agents allows for rapid and long-term mood stabilization in most patients while minimizing potential side effects.

REFERENCES


