Treatment of Bipolar Disorder

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Management strategies for bipolar disorder often entail relatively long-term, complex medication regimens that combine primary mood stabilizers, antipsychotic agents, antidepressants, and other medications, such as benzodiazepines. New strategies for the management of bipolar disorder have recently been evaluated in controlled clinical trials, including using newer anticonvulsants, replacing conventional antipsychotics with atypical antipsychotics, and using novel combination treatments. This article provides an overview of current management strategies for patients with bipolar disorder and describes how these approaches can be incorporated into clinical practice.

(J Clin Psychiatry 2003;64[suppl 6]:9–17)

OVERVIEW OF BIPOLAR DISORDER

Despite the increasing availability of treatments for the various phases of bipolar disorder, patients may experience only partial improvement of symptoms. Even with ongoing maintenance phase treatment, nearly 3 in 4 patients with bipolar disorder relapse within 5 years, and many patients without formally defined relapses still exhibit significant residual symptoms.[1] The impact of this unmet need is significant, given the reported high rates (lifetime prevalence = 3.7%) of bipolar spectrum disorders.[2]

The manic phase of bipolar disorder is characterized by a period of abnormally and persistently elevated, expansive, or irritable mood.[3] This period of mood disturbance includes additional symptoms, such as decreased need for sleep, increased talkativeness, and psychomotor agitation or retardation. The depressed phase often includes reverse vegetative signs, such as weight gain or hypersomnolence, and differs from unipolar depression in several respects, including earlier age at onset, more even gender distribution, higher frequency of episodes, increased likelihood of psychotic symptoms, and a greater risk of suicide.[4]

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Presented at the roundtable discussion "Bipolar Disorder: From Clinical Research to Therapeutic Intervention," which was held June 30, 2001, in Berlin, Germany, and supported by an unrestricted educational grant from AstraZeneca Pharmaceuticals, L.P.

Dr. Nasrallah has been a consultant for, has received honoraria from, and has been on the speakers/advisory boards for Abbott, AstraZeneca, Bristol-Myers Squibb, Janssen, and Pfizer and has received grant/research support from AstraZeneca, Janssen, and Pfizer.

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TYPES OF BIPOLAR DISORDERS

Bipolar I and Bipolar II

In the United States, bipolar disorder has traditionally been classified as bipolar I or bipolar II disorder.[5] More recently, experts in the management of bipolar disorder have increasingly viewed the disorder as a complex cluster of related disorders, in which bipolar I disorder is considered to be the archetypal manifestation of the disease. Beyond bipolar I disorder is a spectrum of other related but less well defined symptom clusters, which can present with depressive features, manic features, mixed states (which satisfy the full diagnostic criteria for both a manic episode and a depressive episode), and varying degrees of severity.

Rapid Cycling

Rapid cycling is defined in the *Diagnostic and Statistical Manual of Mental Disorders* (DSM) as the presence of 4 or more distinct mood episodes (i.e., manic, mixed, depressed, or hypomanic) in 1 year. Rapid-cycling bipolar disorder can be divided into 2 types: primary and secondary rapid cycling. Primary rapid cycling refers to either rapid cycling in the absence of provoking factors or continued rapid cycling in patients who have been free of provoking factors for some time. Secondary rapid cycling refers to rapid cycling associated with some other cause, such as substance abuse or hypothyroidism.

Several factors have been shown to be associated with a high risk of rapid cycling. Women are more likely than men to experience rapid cycling, even though the overall prevalence of bipolar disorder is similar for men and women. Other risk factors for rapid cycling include previous exposure to antidepressants, hypothyroidism, and

older age. Studies in North America typically report a higher incidence of rapid cycling than studies in Europe. This difference may be attributable, at least in part, to the reliance on clinical samples seen at specialized bipolar clinics in the United States, possibly creating a selection bias toward more severely ill patients in some U.S. studies.

COMORBIDITY IN BIPOLAR DISORDER

A recent study examined lifetime and current comorbid Axis I disorders in 288 outpatients with DSM-IV bipolar I or bipolar II disorder.[6] These outpatients satisfied the diagnostic criteria for an average of 0.5 current and 1.7 lifetime Axis I disorders (other than bipolar disorder). Twenty-four percent of patients had a lifetime history of 3 or more comorbid Axis I disorders, the most common of which reported were anxiety and substance abuse disorders. Current and lifetime comorbid anxiety disorders were reported for 30% and 42% of patients, respectively (with panic disorder/agoraphobia and social phobia most common). Current and lifetime comorbid substance abuse disorders were reported for 4% and 42% of patients, respectively (with alcohol and marijuana abuse most common). A current comorbid condition was usually a predictor of several indicators of relatively poor outcome, including limited occupational functioning, a rapid-cycling course, and worsening severity of bipolar episodes over time.

PHARMACOLOGIC TREATMENT OPTIONS FOR BIPOLAR DISORDER

Mood Stabilizers

Mood stabilizer is not a term used by regulatory authorities, nor has any drug ever been designated as a mood stabilizer in its indication. However, the term is often used by clinicians and investigators to refer to a range of classes and specific compounds for the treatment of bipolar disorder and other mood disorders, in particular compounds that are effective in preventing relapse in unipolar or bipolar disorder.

One definition of *mood stabilizer* frequently used in research is any agent capable of treating and/or preventing manias or depressions without causing or exacerbating them.[7] More specifically, mood stabilizers have been defined as medications that reduce the frequency and/or severity of manic, hypomanic, depressive, or mixed episodes in patients with bipolar disorder without exacerbating other mood symptoms.[8] According to treatment guidelines, a mood stabilizer must show efficacy in the treatment of acute mania and/or depression and the prophylaxis of subsequent manic or depressive episodes, not worsen mood symptoms or acute episodes, and not increase the likelihood of an affective switch or cycling.[9] Lithium, divalproex sodium (valproate), and carbamazepine are considered mood stabilizers using these definitions. Lamotrigine may be a possible mood stabilizer for patients with bipolar depression.

Lithium. Placebo-controlled clinical trials conducted during the 1970s found that lithium prophylaxis significantly decreases the frequency of new manic and/or depressive episodes, although subsequent naturalistic studies found that the beneficial effects of lithium in actual clinical practice are often limited.[10] More recent studies have found that 42% to 64% of patients with bipolar disorder do not respond to lithium treatment.[11] The effectiveness of lithium prophylaxis appears to be dose dependent. Gelenberg and colleagues[12] reported that a lithium dose that was adjusted to maintain a target serum concentration of 0.8 to 1.0 mmol/L was more effective at preventing relapse than a lower dose targeted to maintain a serum lithium concentration of 0.4 to 0.6 mmol/L. However, the higher dose was associated with an increased incidence of side effects, including tremor, diarrhea, weight gain, increased urinary frequency, and altered taste.

Although lithium has long been used for the treatment of bipolar disorder, it presents a number of potential limitations. Of particular concern is the observation that lithium discontinuation often produces an abrupt increase in manic or depressive symptoms. The risk of "rebound" when a previously successful long-term maintenance treatment is abruptly discontinued was examined in a meta-analysis[13] which found that discontinuation of lithium treatment was associated with a 28-fold greater monthly risk of new bipolar episodes than among patients who continued to take lithium. The analysis also found an earlier and greater risk of rebound mania than of depression. However, the risk of rebound can be reduced by a gradual down-titration of lithium dose, ideally over several months.

Several other potential limitations of lithium treatment have been described.[8] Lithium is associated with toxicity at doses that are close to its therapeutic range. The most common side effects during acute treatment include gastrointestinal irritation, tremor, and cognitive dulling; with long-term treatment, renal, thyroid, and cardiovascular side effects may occur. Several subgroups of patients do not respond well to treatment with lithium, including patients with mixed states, personality disorders, comorbid substance abuse, mania secondary to other medical conditions, rapid cycling, or previous failed trials of lithium.[8,10,11] It has also been shown that the response to lithium is reduced among patients with 11 or more previous manic episodes or 4 or more depressive episodes, regardless of whether the patient had a history of rapid cycling or mixed states.[14] Finally, many patients discontinue their lithium use after a relatively short period of time. In an analysis of data from a large health maintenance organization, half of patients prescribed lithium discontinued it within about 10 weeks,

and discontinuation was associated with an increased likelihood of psychiatric hospitalizations.[15]

Anticonvulsants. Anticonvulsants, such as divalproex or carbamazepine, are widely used for the acute treatment and long-term maintenance therapy of patients with bipolar disorder. In a rigorous, randomized, double-blind, parallel-group trial,[16] 179 patients hospitalized for acute mania were randomly assigned to a 3-week course of treatment with lithium, divalproex, or placebo. Lithium and divalproex each significantly improved patient scores on the Schedule for Affective Disorders and Schizophrenia–Change Version (SADS-C) manic syndrome subscale. Improvement of at least 50% in SADS-C score was noted for 25% of placebo-treated patients versus 48% of divalproex-treated patients ($p = .04$) and 49% of lithium-treated patients ($p = .025$). Bowden and colleagues[17] compared the effectiveness of lithium and divalproex for maintenance therapy in a randomized, double-blind, placebo-controlled clinical trial in patients with bipolar I disorder. Lithium, divalproex, and placebo groups did not differ significantly from one another on the study's primary endpoint, the time to developing any mood episode. However, compared with placebo, divalproex significantly reduced the number of patients who discontinued the study because of manic or depressive symptoms, and divalproex was significantly more effective than either lithium or placebo on other secondary measures of mood disturbance. Divalproex is also similar or superior to lithium for the treatment of patients with mixed mania[8] and is often used in relatively high doses in an attempt to produce the fastest possible treatment response. Although few controlled studies support the use of this strategy, it is usually viewed as a relatively low risk treatment option, as divalproex is generally well tolerated.

The long-term prophylactic effectiveness of carbamazepine, lithium, and the combination was evaluated in 52 patients with bipolar disorder.[18] In the first year of this 3-year study, patients were randomly assigned to treatment with either carbamazepine or lithium; in the second year, treatments were reversed; and in the third year, patients received the combination of both drugs. The number of patients with "marked" or "moderate" improvement was similar for the 2 monotherapies (33.3% with lithium, 31.4% with carbamazepine) but was greater with combination therapy (55.2%), although the differences were not significant. On several outcome measures, lithium produced significantly greater improvement than did carbamazepine (including decreased total time with manic symptoms, lower average mania severity, and fewer manic episodes per year). This and several other clinical trials suggest that monotherapy with carbamazepine is of limited use for long-term prophylaxis.[19]

Other anticonvulsants have not been evaluated as extensively for the treatment of bipolar disorder. Topiramate, a relatively new anticonvulsant, has been found to improve manic symptoms in small open-label studies.[20,21] Gabapentin is not recommended for the treatment of mania.[22] Lamotrigine is not recommended for the treatment of acute mania, although several studies have shown that it significantly improves symptoms in patients with bipolar depression.[23] Valproate and lamotrigine are considered the best monotherapy treatment options for rapid cycling.[21] However, augmentation with lithium, carbamazepine, atypical antipsychotics, and selective serotonin reuptake inhibitors (SSRIs) is frequently needed. Data from placebo-controlled trials also support the role of lamotrigine for long-term treatment of rapid cycling, particularly in patients with bipolar II disorder. The 2002 revised American Psychiatric Association (APA) practice guidelines recommend lamotrigine as a first-line treatment for bipolar depression, with moderate clinical confidence.[24,25]

Antipsychotics

In Europe, monotherapy with an antipsychotic agent appears to be a more common first-line treatment for severely ill hospitalized patients with bipolar disorder, whereas in the United States psychiatrists are more likely to initiate treatment with a combination of an antipsychotic agent and a mood stabilizer.

Typical antipsychotics. Conventional, or typical antipsychotics, such as haloperidol, have antimanic efficacy, especially in patients who are severely agitated.[26] However, some reports suggest that they have the potential to induce depression in patients with bipolar disorder.[19,27] In addition, it is generally accepted that patients with bipolar disorder are especially vulnerable to the extrapyramidal motor symptoms (EPS), especially tardive dyskinesia (TD), that are strongly associated with the use of typical antipsychotics.[28]

Atypical antipsychotics. Atypical antipsychotics have recently emerged as an alternative to conventional antipsychotics for the treatment of bipolar disorder. They have been shown to be at least as effective as conventional agents for the treatment of mania, but are less likely to cause serious EPS.[29] Although no large randomized, prospective studies have directly compared the efficacy of different atypical agents in bipolar disorder, the evidence available from several recent individual trials suggests that these agents are similar in their effectiveness. In a retrospective chart review of patients who had been treated with clozapine, risperidone, or olanzapine, similar clinical effectiveness was noted with all 3 medications.[30]

Table 1 lists the available double-blind studies that support the use of atypical antipsychotics in the treatment of acute mania. The most extensively evaluated atypical antipsychotic for the treatment of bipolar disorder is olanzapine. Several studies have demonstrated that olanzapine is equivalent in efficacy to haloperidol but more effective than placebo or lithium in treating patients with mania (Table 1).[32–34,39]

Table 1. Randomized, Double-Blind Trials Supporting the Use of Atypical Antipsychotics for the Treatment of Acute Bipolar Mania

Study	Subjects/Diagnosis	Duration, wk	Results[a]
Segal et al, 1998[31]	Inpatients with DSM-IV mania (N = 45)	4	Risperidone = haloperidol = lithium
Tohen et al, 1999[32]	Patients with DSM-IV bipolar I disorder, manic or mixed (N = 139)	3	Olanzapine > placebo
Berk, 1999[33]	Patients with DSM-IV bipolar I disorder, manic (N = 30)	4	Olanzapine = lithium
Tohen et al, 2000[34]	Patients with DSM-IV bipolar I disorder, manic or mixed (N = 115)	4	Olanzapine > placebo
Tohen et al, 2002[35]	Patients with DSM-IV bipolar I disorder, manic or mixed (N = 344)	6	Olanzapine + lithium/divalproex > placebo + lithium/divalproex
Keck et al, 2000[36]	Inpatients with acute mania (N = 195)	3	Ziprasidone > placebo
Zajecka et al, 2000[37]	Patients with DSM-IV bipolar I disorder, manic or mixed (N = 120)	12	Olanzapine = divalproex at 3 weeks; only safety data reported to week 12
DelBello et al, 2002[38]	Adolescents with bipolar I disorder, manic or mixed (N = 30)	6	Quetiapine + divalproex > divalproex + placebo
Tohen et al, 2001[39]	Patients with DSM-IV bipolar I disorder, manic or mixed (N = 453, acute; N = 298, continuation phase)	6 acute + 6 continuation	Olanzapine = haloperidol at week 6 Olanzapine > haloperidol at week 12
Sachs et al, 2002[40]	Patients with DSM-IV bipolar I disorder, manic or mixed (N = 156)	3	Risperidone + lithium/divalproex = haloperidol + lithium/divalproex > placebo + lithium/divalproex
Sachs et al, 2002[41]	Patients with DSM-IV bipolar disorder, manic (N = 190)	3	Quetiapine + lithium/divalproex > placebo + lithium/divalproex
Tohen et al, 2002[42]	Patients with DSM-IV bipolar disorder, manic or mixed (N = 251)	3	Olanzapine > divalproex
Jody et al, 2002[43]	Patients with bipolar I disorder, acute mania (N = 262)	3	Aripiprazole > placebo

[a]Symbols indicate statistical significance at primary efficacy endpoint.

In a 3-week double-blind study, 139 patients were randomly assigned to olanzapine or placebo. Significantly greater improvement from baseline on the Young Mania Rating Scale (YMRS) was noted with olanzapine than with placebo, in patients either with or without psychotic features.[32] The investigators also noted improvement with olanzapine on several secondary endpoints.

A 49-week open-label extension of this study[44] demonstrated that long-term treatment was associated with continued additional improvement beyond that attained in the initial 3-week study for symptoms of mania and depression. The most common side effects of olanzapine were depression, somnolence, and weight gain. The mean weight gain in olanzapine-treated patients was 6.64 kg (14.61 lb) ($p < .001$) during an average treatment period of 6.6 months.

In a second double-blind study, which focused on multiple-episode patients,[34] placebo-treated patients exhibited a mean improvement from baseline on the YMRS of 8.1 points, compared with an average improvement of 14.8 points with olanzapine ($p < .001$). Olanzapine also significantly improved several secondary measures of bipolar disorder severity.

In a recent study of 251 manic or mixed patients, Tohen et al.[42] found that olanzapine was significantly more effective than divalproex in treating acute manic symptoms at the end of 3 weeks. This is in contrast to a longer-term study (12 weeks) by Zajecka et al.[37] in which olanzapine and divalproex were determined to have equal efficacy in treating manic symptoms. The difference was thought to be related to the sample size. Side effects of olanzapine in both trials were significantly greater than of divalproex and included weight gain, depression, dry mouth, and somnolence.

Risperidone has also been shown to improve symptoms in bipolar disorder. In a randomized, double-blind, 4-week trial, risperidone produced improvement in manic symptoms similar to lithium and haloperidol on several clinical rating scales.[31] In a small, open-label pilot study, risperidone improved the manic, depressive, and mixed symptoms of patients with rapid cycling refractory to treatment with lithium, carbamazepine, and valproate.[45] The efficacy and safety of risperidone versus haloperidol in combination with a mood stabilizer (lithium or divalproex) was assessed in a 3-week randomized, placebo-controlled trial.[40] This study demonstrated that patients treated with risperidone or haloperidol and a mood stabilizer (lithium/divalproex) had significantly greater reductions in YMRS scores at the end of the study and over time compared with placebo-treated patients. The number of patients reporting EPS in the risperidone group was significantly greater and 3 times that in the placebo group. There was also significant weight gain in the risperidone group (mean weight gain = 2.41 kg [5.3 lb], $p < .004$) over the 3-week treatment period. Similarly, in another add-on study, risperidone treatment over a period of 3 weeks resulted in greater improvement of manic symptoms compared with placebo.[46]

Quetiapine is an atypical antipsychotic commonly used in clinical practice. Its use for the treatment of schizophre-

nia is already approved in many countries, and preliminary reports suggest that it is effective in bipolar disorder. Chisholm and colleagues[47] conducted a retrospective study of 15 patients with bipolar I or bipolar II disorder who had been prescribed quetiapine as an adjunctive medication. Response was assessed over a period of 2 weeks to 6 months. Quetiapine improved symptoms in most patients, although the small number of patients precluded statistical analyses of the results. Sedation was the most common adverse event. A small randomized, double-blind pilot study found that in adolescent patients with mania, quetiapine in combination with divalproex improved symptoms more than divalproex alone.[38] In an open-label follow-up study in patients with rapid-cycling bipolar disorder, quetiapine with or without a concomitant mood stabilizer appeared to be effective.[7]

Results from the first large, multicenter, randomized, controlled study of quetiapine as add-on therapy with lithium or divalproex in acute bipolar mania suggest that it has superior efficacy when used as an adjunct to treatment compared with lithium or divalproex alone.[48] Treatment with quetiapine resulted in a significant improvement in manic symptoms, with a mean change in score on the YMRS of –13.76 and –9.93 for the quetiapine- and placebo-treated groups, respectively ($p = .021$). Response rates at final assessment were 54.3% and 32.6% ($p = .005$). Reduction in the Clinical Global Impressions scale for bipolar disorder severity score was also significantly greater at the last assessment for the quetiapine group than for the placebo group (–1.38 and –0.78, respectively; $p = .001$). The most common adverse events in quetiapine-treated patients were somnolence, dry mouth, asthenia, and postural hypotension. Discontinuations due to adverse events were similar in each group and were numerically slightly higher in the group taking lithium or divalproex alone.

Preliminary results for the atypical antipsychotics ziprasidone and aripiprazole also suggest that these drugs are more effective than placebo in the treatment of patients with acute mania.[36,43] Despite some initial anecdotal reports suggesting that atypical antipsychotics may be associated with induction of mania, controlled prospective clinical trials have not shown that these agents cause an increase in manic symptoms.[49] Unlike conventional agents, atypical antipsychotics do not appear to induce depression in manic patients, as evidenced in a recent randomized, double-blind, placebo-controlled trial of quetiapine.[41] Large-cohort data from a comparison of risperidone, quetiapine, and clozapine in patients enrolled in the Stanley Bipolar Network indicate that all 3 agents were associated with improvement in Hamilton Rating Scale for Depression (HAM-D) scores over 3 months of treatment; improvement was significantly greater with quetiapine than with risperidone or clozapine.[50] In the QUEST clinical trial, an open-label comparison of quetiapine and risperidone in outpatients with psychotic and mood disorders, quetiapine produced significantly greater improvement than risperidone on HAM-D scores.[51]

In general, the risk of EPS and TD appears to be lower with the atypical antipsychotic agents than with conventional antipsychotics, although there are potential causes for concern in other areas. Olanzapine is associated with a risk of significant weight gain, diabetes, and ketoacidosis.[30,52] Risperidone is associated with dose-dependent increases in prolactin and EPS. Risperidone has also been shown to be rapidly eliminated from circulation among patients treated with carbamazepine, suggesting a potentially clinically significant interaction between these 2 drugs, probably as a result of the induction of cytochrome P450 enzyme–mediated metabolism by carbamazepine.[53] Quetiapine is associated with fewer EPS and less weight gain than other atypical antipsychotics, but some patients may experience somnolence.[41] However, somnolence may prove to be beneficial in patients who are manic or aggressive.

Antidepressants

Although antidepressants are clearly effective for the treatment of unipolar depression, their role in the management of depressive symptoms in bipolar disorder is under debate. Any clear efficacy of antidepressants in bipolar depression[54,55] must be balanced against their tendency to induce "switching" into mania. Conversely, it can be argued that patients with moderate or severe acute bipolar depression and those who do not respond to the relatively weaker antidepressive efficacy of lithium and other traditional mood stabilizers[56] often need a highly effective antidepressive treatment.[57] Modern antidepressants like the SSRIs appear to have a much lower risk of inducing switch to mania compared with tricyclic antidepressants (TCAs). Given the established high risk of suicide in bipolar depressed patients, the rapid and effective resolution of depression is an unmet need that underlies the demand for the prescription of antidepressants. Generally, the antidepressant should be combined with a mood stabilizer to reduce the risk of switching. The APA guidelines recommend combination of an antidepressant with a mood stabilizer as a second-line approach for severely depressed patients with life-threatening behavior,[58] while the World Federation of Societies of Biological Psychiatry (WFSBP) guidelines view this as a first-line approach for all depressed patients, not only those with severe bipolar depression.[57] The WFSBP guidelines reflect the views of several European experts.

No data show that the combination of lithium or other mood stabilizers with an antidepressant increases other antidepressive responses in acute bipolar depression.[19,59,60] However, recent data available from the Stanley Bipolar Network indicate that this combination in a 1-year-follow-up was superior in preventing depressive relapses compared with long-term monotherapy with a mood stabi-

lizer.[61] Tricyclic antidepressants in particular induce switching and may lead to rapid cycling in a certain percentage of patients. Antidepressants should be avoided in patients with rapid cycling. In a detailed analysis of the course of illness of 51 patients with lithium-refractory bipolar disorder, 35% of patients had 1 or more episodes of cycle acceleration thought likely to be related to the use of heterocyclic antidepressants.[62]

The use of monoamine oxidase inhibitors (MAOIs) is often limited by side effects, by the requirement that the patient adhere to a restrictive tyramine-free diet, and by the fact that these agents may cause cycle acceleration or induce mania in many patients.[62] If an antidepressant is required, SSRIs are often chosen because of their ease of use, low toxicity in overdose, and relatively low likelihood of inducing a switch to mania or hypomania.[4] Bupropion is a reasonable alternative because it possesses a relatively low risk of weight gain, sexual side effects, and switch to mania.[4] Limited data are available regarding the use of other newer antidepressants in bipolar disorder. The efficacy of some atypical antipsychotics for the treatment of acute bipolar depression has also been explored, with promising results. Some data suggest that the combination of an atypical antipsychotic and an SSRI is more effective than either agent alone for treatment-resistant depression.[63] However, these preliminary results need confirmation in controlled, randomized clinical trials.

Other Medications

Other adjunctive medications are used in bipolar disorder, including benzodiazepines (to manage comorbid anxiety or to provide an immediate sedative effect for patients who are very agitated) and anticholinergic medications (to manage movement-related side effects of conventional antipsychotics).

MANAGEMENT RECOMMENDATIONS BASED ON APA GUIDELINES

Several international guidelines are available for the management of patients with bipolar disorder. Most have similar recommendations but may differ in some aspects, such as in the treatment of acute bipolar depression, as mentioned earlier in this review.[24,57] The following is a summary from the recently revised APA guidelines of recommendations for treatment of patients with bipolar disorder.[24]

Manic/Mixed Episodes

A mood stabilizer (lithium or divalproex) plus an antipsychotic (preferably an atypical) is recommended for patients with severe manic or mixed episodes, with divalproex being preferable for patients with mixed episodes. Monotherapy with lithium, divalproex, or an antipsychotic is the treatment of choice for patients who are not severely ill. Carbamazepine and oxcarbazepine are alternative mood stabilizer choices. It is recommended that any antidepressants in use be tapered and discontinued. In patients who experience manic or mixed episodes despite treatment (a "breakthrough" episode), medication dose should first be optimized, with an atypical antipsychotic resumed or added as necessary. Benzodiazepines are recommended as short-term adjunct treatment for patients who are severely ill or agitated. Second-line treatment consists of addition of another first-line medication, or adding/switching atypical antipsychotics. Clozapine and electroconvulsive therapy (ECT) may be effective for treatment-resistant patients. ECT is also an option for patients with mixed episodes and pregnant women experiencing severe mania. Antipsychotics are recommended for patients with manic or mixed episodes with psychotic features.

Depressive Episodes

For patients with severe depressive episodes, treatment with lithium or lamotrigine is recommended as first-line therapy, with a combination of lithium and an antidepressant as an alternative choice. Monotherapy with antidepressants is not recommended. ECT is recommended for severely depressed patients, including pregnant women and those with psychotic features. For patients with breakthrough episodes, optimizing dose of medication should be the first option. If acutely depressed patients are nonresponsive to first-line options, addition of lamotrigine, bupropion, or paroxetine is recommended. Alternatively, another SSRI, venlafaxine, or an MAOI may be added. Because bipolar II patients are at decreased risk of antidepressant-induced hypomania, antidepressants may be initiated at an earlier stage than in bipolar I patients. An antipsychotic or ECT is the treatment of choice for depressed patients with psychotic features.

Rapid Cycling

For many patients with rapid cycling, combination treatment is favored over monotherapy, with lithium or divalproex as first-line monotherapy options and lamotrigine as an alternative choice. Prior to first-line therapy, medical conditions that may have precipitated rapid cycling, e.g., hypothyroidism and substance abuse, should be identified and treated. Since some medications, particularly antidepressants, are also associated with increased risk of rapid cycling, these medications should be gradually discontinued.

Maintenance Treatment

It is generally recommended that patients continue treatment after an acute episode has subsided. The APA guidelines recommend lithium or divalproex as first-choice continuation/maintenance treatment. Lamotrigine, carbamazepine, or oxcarbazepine are possible alternatives. It is advisable to continue these medications if patients were already being treated with one of these options. Cur-

rently approved antipsychotics should be discontinued unless necessary for control of persistent psychosis or as prophylaxis. For subthreshold symptoms or breakthrough episodes, the addition of an atypical antipsychotic or an antidepressant may be warranted. ECT may also be considered useful maintenance therapy for those patients who have responded to it previously.

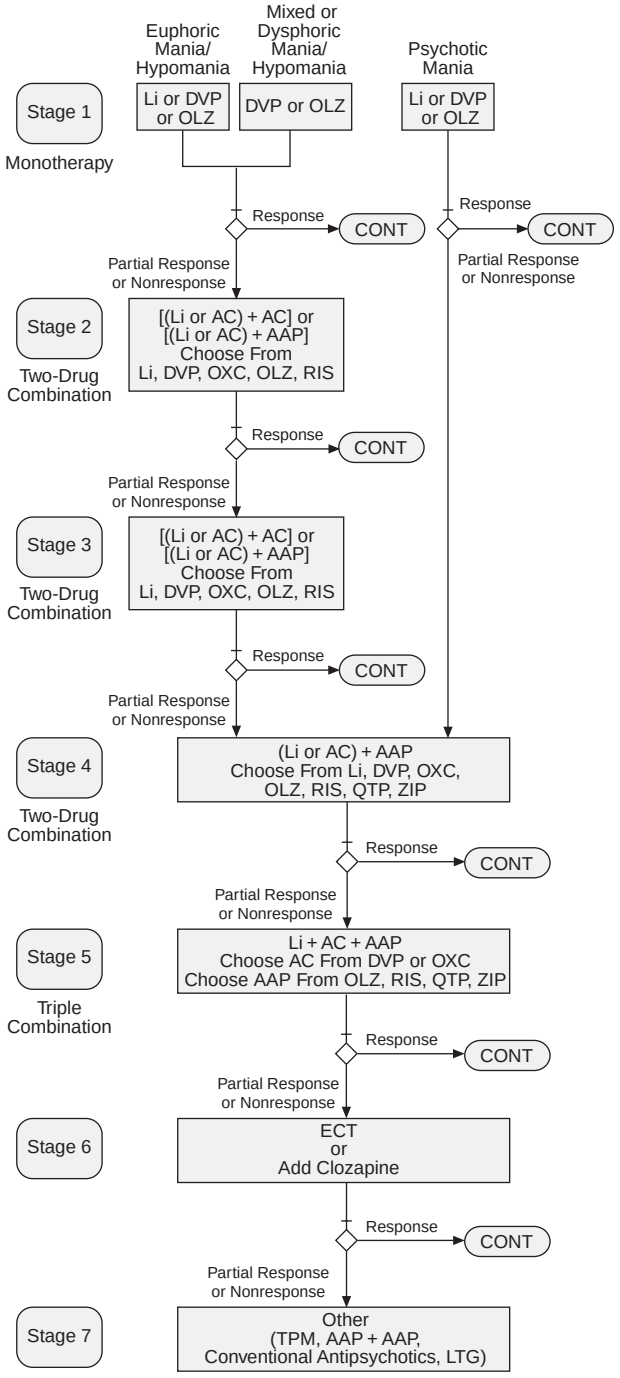
Psychosocial interventions, such as interpersonal therapy and cognitive-behavioral therapy, are recommended as additions to pharmacotherapy with moderate clinical confidence for bipolar depressed patients, but are less likely to be effective in patients with acute mania.

The Texas Medication Algorithms for Bipolar Disorder

Recently, sequential treatment algorithms with similar recommendations as the APA guidelines have also been developed for bipolar disorder. One such initiative in Texas has resulted in algorithms for mania/hypomania and depressive episodes.[64] The algorithm for mania/hypomania focuses on the treatment of core symptoms only. Monotherapy with lithium, divalproex, or olanzapine is recommended as a first-line option for patients diagnosed with bipolar I disorder with mania or hypomania, and with symptoms severe enough to warrant medication (Figure 1). At the time these algorithms were developed, most data from placebo-controlled trials were available for olanzapine, so it became the preferred atypical antipsychotic. Positive data have since emerged for several other atypical antipsychotics, such as risperidone, quetiapine, ziprasidone, and aripiprazole (Table 1). Combination therapy, rather than switching medication, is recommended for those patients who partially respond but are tolerant to monotherapy. Patients intolerant to monotherapy should be treated with an alternative mood stabilizer before attempting combination therapy. Second-line treatment recommendations include combination of 2 drugs: either lithium/anticonvulsant plus an anticonvulsant or lithium/anticonvulsant plus an atypical antipsychotic. Figure 1 further describes management strategies for patients who do not respond to second-line treatment options, including the addition of a second atypical antipsychotic to the above combination therapy and ECT for acute mania.

The algorithm for treating depression in patients with bipolar disorder directs clinicians to use the recommendations as concomitant treatment to any stage of treatment of mania/hypomania. If a patient has significant depressive symptoms, an attempt should first be made to initiate or optimize the use of mood stabilizers. An SSRI, bupropion, or lamotrigine can be added for those patients with severe depressive episodes requiring treatment. Further options for severely depressed patients include therapy with a different class of antidepressant or the use of 2 antidepressants. MAOIs or the addition of an atypical antipsychotic is recommended if the above medications are not satisfactory.

Figure 1. Algorithm for the Treatment of Mania or Hypomania in Patients With Bipolar I Disorder[a]



Abbreviations

Li = Lithium
AC = Anticonvulsant
DVP = Divalproex
LTG = Lamotrigine
OXC = Oxcarbazepine
TPM = Topiramate
AAP = Atypical Antipsychotic
OLZ = Olanzapine
RIS = Risperidone
QTP = Quetiapine
ZIP = Ziprasidone
ECT = Electroconvulsive Therapy
CONT = continue

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For maintenance treatment, both algorithms advocate continuing for at least 1 to 3 months the therapy that the patient was receiving for the acute episode, with a gradual simplification of the treatment regimen as the patient continues to be stable.

Preliminary results indicate that these algorithms, which are based on expert consensus opinion and reflect current treatment options for bipolar disorder, have been successfully implemented in various health care organizations in Texas.[65] It is hoped that such treatment algorithms will improve the consistency of treatment in patients with bipolar disorder, optimize the use of existing medications, and thus lead to better outcomes for patients with bipolar disorder.

SUMMARY

The 2 major phases of bipolar disorder are mania and depression. Management of bipolar disorder is complicated by underrecognition, underdiagnosis, misdiagnosis, and comorbidity with other mood, anxiety, and psychotic disorders. However, pharmacologic treatment options are increasingly becoming available. Traditional mood stabilizers, such as lithium, carbamazepine, and divalproex, and typical antipsychotics, such as haloperidol, have been widely used for acute and long-term treatment, but typical antipsychotics are associated with a high burden of side effects, such as EPS and tardive dyskinesia. More recently developed atypical antipsychotics have a reduced side effect burden compared with conventional (typical) antipsychotics. Efficacy against manic symptoms has been reported for olanzapine, risperidone, quetiapine, ziprasidone, and aripiprazole. The anticonvulsant lamotrigine shows promise in the treatment of bipolar depression. Antidepressants are effective for unipolar depression, but they may induce switching to mania, so their use as monotherapy in bipolar depression is not recommended. Antidepressants may be useful in combination with atypical antipsychotics to treat bipolar depression, but further studies are required to confirm the utility of this approach. Current recommendations for management of bipolar disorder include initiating treatment with a mood stabilizer and an atypical antipsychotic for patients with mania, and the addition of an antidepressant for those in the depressive phase.

Drug names: aripiprazole (Abilify), bupropion (Wellbutrin and others), carbamazepine (Carbatrol, Tegretol, and others), clozapine (Clozaril and others), divalproex sodium (Depakote), gabapentin (Neurontin), haloperidol (Haldol and others), lamotrigine (Lamictal), olanzapine (Zyprexa), oxcarbazepine (Trileptal), paroxetine (Paxil), quetiapine (Seroquel), risperidone (Risperdal), topiramate (Topamax), venlafaxine (Effexor), ziprasidone (Geodon).

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