



# Focus on Bipolar Disorder Treatment

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## Acute Mania Treatment

In recent years, there have been some remarkable advances in the treatment of bipolar disorder and, specifically, in the treatment of acute mania, stated Terence A. Ketter, M.D. Effective acute mania treatment is particularly important because mania causes many of the social and external difficulties that patients with bipolar disorder experience. The irritability, impulsivity, risk taking, and poor judgment that accompany manic episodes often bring these patients into conflict with work supervisors, other authorities, and families causing disruption and other problems in the lives of both the patients and the people around them. It is therefore imperative to find treatments that will successfully bring patients having acute manic episodes to recovery.

### Agents Approved for Acute Mania in the United States

Since 2000, there has been a proliferation of agents approved in the United States for treatment of acute mania (Table 1).<sup>1</sup> In addition to the 3 drugs already approved by the U.S. Food and Drug Administration (FDA) (lithium, chlorpromazine, and divalproex), 5 atypical antipsychotics (olanzapine, risperidone, quetiapine, ziprasidone, and aripiprazole) and the anticonvulsant carbamazepine are now officially sanctioned as effective and safe treatments for acute mania in patients with bipolar disorder. There are also now 4 FDA-approved drugs for bipolar disorder maintenance treatment and 1 for acute bipolar depression (Table 1). Generally, a drug is approved by the FDA when its efficacy and safety for a particular indication are supported by 2 multicenter, randomized, double-blind, placebo-

controlled trials with adequate sample sizes.

There have been approximately 15 recent monotherapy studies<sup>2-15</sup> for acute mania, involving over 2300 patients taking an active drug (including lithium, divalproex, carbamazepine, and atypical antipsychotics) and over 1200 patients taking placebo (J. R. Calabrese, M.D.; E. Vieta, M.D.; J. Mullen, M.D.; et al., manuscript submitted). These studies have shown that a significantly greater percentage of patients taking an active drug (approximately 50%) experience at least a 50% decrease in the symptoms of acute mania compared with the patients taking placebo (approximately 30% response). Dr. Ketter pointed out that, in most studies, the patients taking placebo were also receiving a dramatic psychosocial intervention—acute psychiatric hospitalization—and rescue benzodiazepines during the first week of the studies.

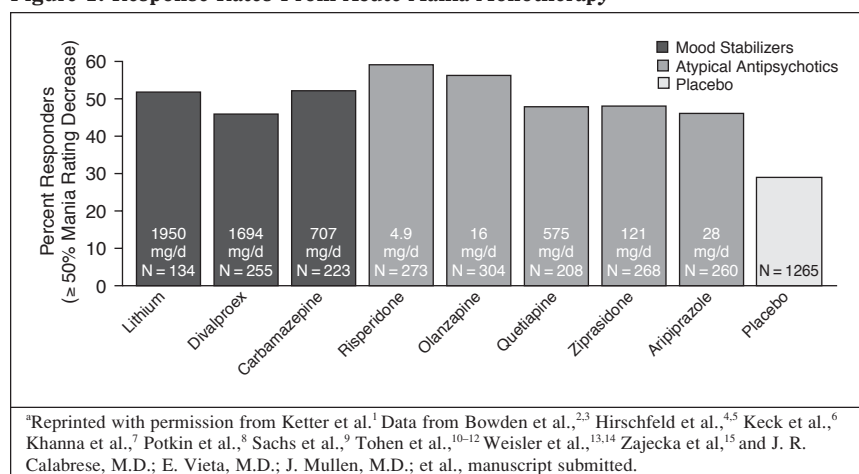
Dr. Ketter reviewed the monotherapy efficacy according to medication and concluded that the response rates were more similar than different. Response rates to the 8 studied pharmacologic monotherapies ranged between 45% and 60%. For the response rates elicited by the individual drugs, see Figure 1 (J. R. Calabrese, M.D.; E. Vieta, M.D.; J. Mullen, M.D.; et al., manuscript submitted).<sup>1-15</sup>

Comparing monotherapy with combination therapy in 5 recent studies<sup>16-19</sup> showed a significantly higher rate of responders among patients receiving combination therapy. In these studies, patients receiving a mood stabilizer (lithium or divalproex) plus an atypical antipsychotic (olanzapine, risperidone, or quetiapine) had a response rate of approximately 60%, while pa-

**Table 1. Agents Approved for Bipolar I Disorder in the United States<sup>a</sup>**

Drug	Year Approved Acute Mania	Year Approved Maintenance	Year Approved Acute Depression
Lithium	1970	1974	
Chlorpromazine	1973		
Divalproex	1994		
Olanzapine	2000 <sup>b</sup>	2004	
Olanzapine-fluoxetine combination			2003
Lamotrigine		2003	
Risperidone	2003 <sup>b</sup>		
Quetiapine	2004 <sup>b</sup>		
Ziprasidone	2004		
Aripiprazole	2004	2005	
Carbamazepine	2004		

<sup>a</sup>Data from Ketter et al.<sup>1</sup>  
<sup>b</sup>Approved for adjunctive as well as monotherapy.

**Figure 1. Response Rates From Acute Mania Monotherapy<sup>a</sup>**

tients receiving a mood stabilizer plus placebo had a response rate of about 40%.

**Anticonvulsants.** Divalproex was the first mood stabilizer to be approved for mania in the modern era. This approval was based on pivotal studies that compared divalproex to placebo. Specifically, a study published by Bowden and colleagues<sup>2</sup> in 1994 compared divalproex, lithium, and placebo and found that both of the active treatments had a response rate of almost 50% (48% for divalproex, 49% for lithium), while 25% of patients taking placebo experienced improvement. Also, divalproex was found to be as effective in rapid-cycling manic patients as in other patients. In this study, the final dose of divalproex was about 2000 mg/day, producing a blood level of about 93  $\mu$ g/mL, and the final dose of

lithium was 1950 mg/day, with a blood level of 1.2 mmol/L. However, later studies<sup>4,15</sup> have found that loading divalproex, starting at 20–30 mg/kg per day, is well tolerated and may yield therapeutic blood levels more quickly.

Although carbamazepine has a long history of clinical use in bipolar disorder, it only recently received an FDA indication. This approval was based on 2 studies<sup>13,14</sup> from Weisler and colleagues. The first study,<sup>13</sup> done in the United States, found the responder rate with carbamazepine at endpoint to be 42%, while the responder rate with placebo was 22%. The second, international study<sup>14</sup> also found carbamazepine to have a greater efficacy, with a response rate of 61% (placebo response rate, 29%). The final dose of carbamazepine in both of these trials was around 700 mg/day, but about

40% of patients had adverse effects at this dosage.

With the exception of divalproex and carbamazepine, newer anticonvulsants have not generally shown efficacy in acute mania. Lamotrigine is effective for maintenance treatment and may have efficacy in patients with depression and rapid cycling. Controlled trials suggest that gabapentin and topiramate are not effective as primary interventions for acute mania, but they may be useful adjuncts for comorbid conditions commonly seen in patients with bipolar disorders. There are inadequate data to determine whether levetiracetam, zonisamide, and oxcarbazepine have efficacy in bipolar disorder treatment.<sup>1</sup>

**Atypical antipsychotics.** Olanzapine was the first atypical antipsychotic to be approved for the treatment of acute mania in patients with bipolar disorder, and that approval was based on 2 studies<sup>10,11</sup> published in 1999 and 2000. The first study<sup>10</sup> had a starting olanzapine dose of 10 mg/day and ending dose of 15 mg/day, and efficacy did not emerge until the end of week 3. In the second study,<sup>11</sup> the starting dose was 15 mg/day, and the ending dose was 16 mg/day, with efficacy being reached at week 1. Dr. Ketter emphasized the importance of aggressively dosing olanzapine to bring about the greatest possible efficacy.

Risperidone has been tested in several double-blind, placebo-controlled trials,<sup>5,7,20</sup> and risperidone monotherapy has proven efficacious in treating acute mania. In most trials, the dose is about 4 mg/day. A study<sup>20</sup> conducted in Moscow compared risperidone with haloperidol and placebo; both active agents were more effective than placebo. The importance of monitoring for extrapyramidal symptoms at higher doses of this drug was stressed by Dr. Ketter.

Double-blind, placebo-controlled trials<sup>3</sup> have also shown efficacy for quetiapine monotherapy in acute mania. In a recent trial by Calabrese and colleagues, quetiapine was started at 100 mg/day and increased daily by 100

mg, with final doses in responders of about 600 mg/day (J. R. Calabrese, M.D.; E. Vieta, M.D.; J. Mullen, M.D.; et al., manuscript submitted).

Studies<sup>8,21</sup> of ziprasidone found it efficacious in treating acute mania when used at adequate doses. The typical day 1 dose for ziprasidone was 80 mg, which was increased to 160 mg on day 2. Mean final dosing was about 130 mg/day. Absorption of ziprasidone doubles when it is taken with food, so the clinician must make sure that the patient takes the medicine with food to ensure adequate dosing.

Aripiprazole was also approved as a result of 2 double-blind, placebo-controlled studies.<sup>6,9</sup> In both trials, the final aripiprazole dose was around 30 mg/day. In some patients, an initial dose of 30 mg can cause nausea, perhaps due to the drug's dopamine receptor partial agonist effect. Reducing the dose to 15 mg/day for a few days in these patients will reduce the nausea; it may be possible to increase the dose to 30 mg afterwards without adverse effect. Both aripiprazole and ziprasidone are non-sedating, and side effects such as sedation and weight gain seem to be less problematic than with some of the older atypical antipsychotics; however, they may sometimes cause akathisia. Dosing should be regulated accordingly.

The efficacy spectra of the atypical antipsychotics seem to have more similarities than differences within the class. In addition to being approved for manic episodes, all of the atypicals except quetiapine, which requires more targeted studies, have received indications for mixed episodes. All of these atypicals seem to be effective in patients with psychotic mania, and at least olanzapine and aripiprazole have been studied and found useful in rapid-cycling patients. Overall, Dr. Ketter characterized the atypical antipsychotics as having a broad efficacy spectrum for bipolar disorder.

### Acute Therapy and Long-Term Outcome

The immediate goals of acute mania treatment are to minimize the danger to

the patient and those around him or her and to control the acute symptoms; however, a clinician must also plan ahead for the successful transition from acute to maintenance care. Poor tolerability to pharmacotherapy compromises effectiveness and can affect short- and long-term outcomes. Since acute care interventions are often continued into long-term treatment, it is important to consider the significant ramifications they can have for the overall health of the patient.

### Safety and Tolerability Considerations

Among the mood stabilizers, lithium, divalproex, and carbamazepine all have boxed warnings for safety concerns. Lithium can cause neurotoxicity, while divalproex can have hepatic and teratogenic effects and contribute to pancreatitis. Carbamazepine has been known to have hematologic adverse effects.

As a class, the atypical antipsychotics have received boxed warnings for sudden death in elderly patients, and this warning reminds clinicians that these medications lack indications for the treatment of agitation in dementia. The FDA has taken the position that atypical antipsychotics increase the risk of hyperglycemia and diabetes. There is some controversy about the degree to which this is problematic for ziprasidone and aripiprazole, but this warning is in the product information of all of the atypicals. Weight gain and sedation are common tolerability problems that can become safety issues.

### Conclusion

Dr. Ketter reiterated that a wide variety of new pharmacologic treatment options exists for bipolar disorder, with diverse mechanistic efficacy and adverse effect profiles. As a class, the new atypical antipsychotics are effective in treating acute mania and are emerging as potentially effective treatments for acute bipolar depression as well as maintenance care for patients with bipolar disorders. In contrast, al-

though the new anticonvulsants have variable efficacy in bipolar disorders and comorbid conditions, they are not effective in acute mania as a class. New agents are presently in development, and a few more years of research should present an even wider array of acute mania treatment options.

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bipolar depression that meet the criteria of Category A evidence, but there have been small double-blind studies of imipramine, bupropion, desipramine, fluoxetine, moclobemide, and tranylcypromine.<sup>5,6</sup> A meta-analysis by Gijsman and colleagues<sup>6</sup> looked at these studies and surmised that standard antidepressants offered efficacy for treatment of bipolar depression; however, much of the benefit was found in the few trials with monoamine oxidase inhibitors, which may make these data less applicable to modern treatment settings.

### 21st Century Bipolar Disorder Research

**Placebo-controlled trials.** There are only a few Category A trials. There have been positive trials of monotherapy with lamotrigine,<sup>7</sup> olanzapine,<sup>8</sup> quetiapine,<sup>9</sup> and olanzapine plus fluoxetine.<sup>8</sup> However, there are negative or failed trials of imipramine monotherapy<sup>10</sup> and the combination therapies of lithium plus paroxetine<sup>11</sup> and lithium plus imipramine.<sup>11</sup> The response rates in these trials are illustrated in Figure 2,<sup>7-9,11,12</sup> showing the placebo response rates and the differences between the active drug and placebo response, the indication of drug effectiveness.

**Randomized comparator trials without placebo control.** Dr. Sachs reviewed 4 randomized comparator trials without placebo control (Category B evidence) of bipolar depression treatments.

In a trial of imipramine versus moclobemide,<sup>13</sup> no statistically significant differences were found on any efficacy measure. Nevertheless, several efficacy trends favored imipramine over moclobemide. Imipramine (13.0 point decrease) produced a greater change from baseline score than moclobemide (9.9 point decrease) on the Hamilton Rating Scale for Depression. Subjects taking imipramine also experienced a greater change from baseline score on the Montgomery-Åsberg Depression Rating Scale than subjects taking moclobemide (17.6 vs. 13.2 point decrease). Although it was

## Treatment of Bipolar Depression

Gary S. Sachs, M.D., described treatment of bipolar depression as the most important bipolar disorder treatment phase due to its frequency and associated level of impairment. Among patients with bipolar I disorder, depressive symptoms predominate over manic/hypomanic symptoms by a ratio of 3:1,<sup>1</sup> and patients with bipolar II disorder experience 37 times more depression than hypomania.<sup>2</sup> During Dr. Sachs's presentation, he emphasized the importance of acute depression care, reviewed the applicable 20th century studies, examined newer evidence and novel approaches, discussed treatment-emergent affective switch, and shared some of the treatment approaches designed by the Systematic Treatment Enhancement Program for Bipolar Disorder (STEP-BD).

STEP-BD has been observing bipolar patients over the past 6 years, and Dr. Sachs reported some of its early prospective findings.<sup>3</sup> Among patients who achieved recovery, STEP-BD found that about 5% relapsed each month, and approximately

80% of those relapses were into a depressive episode. The time between relapses was shorter among those patients who were depressed before recovery than among those who had mania prior to recovering. The median duration of time spent well between episodes was found to be about 3 months. The number of psychiatric hospitalizations in patients with bipolar depression equaled 14.2 per 100 patient years, and the mortality rate was 0.11 per 100 patient years.

### 20th Century Bipolar Depression Research

Examining the research of treatment options for any disorder requires a uniform way of rating the value of the evidence in support of a treatment's efficacy. In evaluating the research for bipolar depression treatment, Dr. Sachs focused primarily on Category A evidence, or randomized, double-blind, placebo-controlled trials with adequate sample sizes. The categories of evidence are delineated in Table 2.<sup>4</sup>

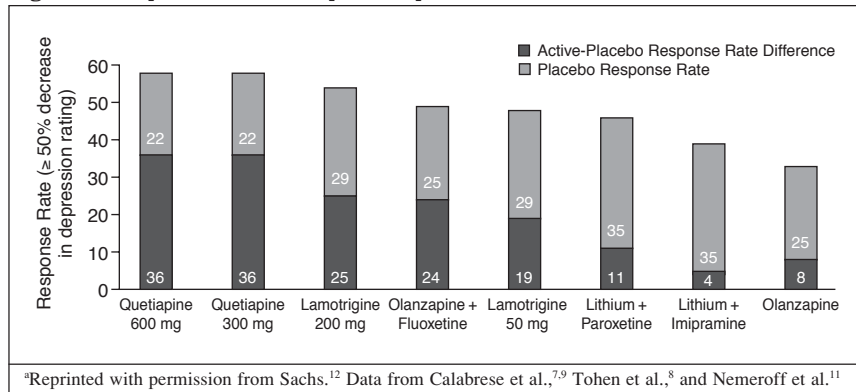
**Antidepressants.** There are no 20th century studies of antidepressants in

**Table 2. Categories of Evidence<sup>a</sup>**

Category A+	> 1 randomized, double-blind, placebo-controlled trial with adequate sample or approval by the FDA or the EMEA
Category A	≥ 1 randomized, double-blind, placebo-controlled trial with adequate sample
Category B	Randomized, double-blind, controlled trial without placebo or with inadequate sample
Category C	Open, controlled trial with (C+) or without (C) randomization with adequate sample
Category D	Uncontrolled series (D) or case report (D-) Equivocal controlled trial
Category E	No published studies, with (E+) or without (E-) evidence of class effect
Category F	Controlled trial with negative result

<sup>a</sup>Based on Sachs.<sup>4</sup>

Abbreviations: EMEA = European Medicines Agency, FDA = Food and Drug Administration.

**Figure 2. Response Rates to Bipolar Depression Treatment<sup>a</sup>**<sup>a</sup>Reprinted with permission from Sachs.<sup>12</sup> Data from Calabrese et al.,<sup>7,9</sup> Tohen et al.,<sup>8</sup> and Nemeroff et al.<sup>11</sup>

not statistically significant, the proportion meeting remission criteria was greater with imipramine than with moclobemide (53% vs. 46%). In terms of treatment-emergent affective switch, more subjects taking imipramine had to withdraw from the study due to mania onset than patients taking moclobemide, but this difference was not significant (11% vs. 3.7%). A greater, though not statistically significant, percentage of patients taking imipramine scored higher than 18 on the Young Mania Rating Scale compared with patients taking moclobemide (6.7% vs. 2.5%). These findings may show moclobemide to be a safer treatment than imipramine.

A study<sup>14</sup> of antidepressants added to mood stabilizers also showed no significant differences in efficacy. Bupropion (up to 450 mg/day), sertraline (up to 200 mg/day), or venlafaxine (up to 375 mg/day) was added to mood-stabilizing treatment. About 37% of patients in each treatment group had

much or very much improved scores on the Clinical Global Impressions-Bipolar Disorder scale for the depression item, and treatment-emergent affective switches were reported fairly equally across the treatment groups, in about 14% of the total number of patients. Many (N = 73) of the acute responders participated in a 1-year continuation treatment study. Although 35.6% of participants reported treatment-emergent affective switches, only 16.4% of these responders had clinically significant hypomania or mania. The remaining 19.2% experienced milder hypomania that resulted in minimal to no dysfunction.

Vieta and colleagues completed a 6-week randomized, single-blind comparison<sup>15</sup> in which subjects participating in ongoing mood stabilizer treatment with lithium, valproate, carbamazepine, or other putative mood stabilizers were given adjunctive paroxetine (N = 30) or venlafaxine (N = 30). Since the paroxetine re-

sponse rate was 43% and the venlafaxine response rate was 47%, there was no statistically significant difference in efficacy. However, there was a substantially greater rate of treatment-emergent affective switch reported by patients taking venlafaxine (13%) compared with patients taking paroxetine (3%).

**Naturalistic comparison studies without randomization.** Naturalistic comparison studies without randomization must be considered quasi-experimental. Although they may be useful in the absence of true experimental data, they do not permit confident causal interpretation of the statistical analyses.

Altshuler and colleagues<sup>16</sup> followed 1000 patients in the Stanley Bipolar Research Network, focusing on 84 subjects who had achieved remission from a depressive episode with a mood stabilizer and adjunctive antidepressant. Approximately half of that subset (43 subjects) stopped antidepressant treatment within 6 months of remission, and 70% of them experienced a depressive relapse within a year compared with 36% of the 41 subjects who maintained antidepressant treatment for more than 6 months after remission. However, the initial response rate to antidepressants was only 15%, continuing to decrease throughout the follow-up year.

Although the STEP-BD includes a randomized, double-blind trial, Dr. Sachs and the other researchers completed a naturalistic comparison study<sup>3</sup> of the outcome data from people who did not agree to be in the official trial or who were not eligible for randomization. When comparing the people taking adjunctive antidepressants with those who were not taking them, the recovery rates were nearly identical, both around 25%. The rate of switching to manic, hypomanic, or mixed episodes was slightly higher for people taking antidepressants than for those who were not, but the difference was not significant (18% vs. 11%). Dr. Sachs suggested that this slightly elevated switch risk might be worth

**Table 3. Systematic Treatment Enhancement Program for Bipolar Disorder (STEP-BD) Acute Bipolar Depression Treatment Pathway<sup>a</sup>**

Decision Point	Initial Management Recommendation	
1. Determine need for acute phase antidepressant treatment	Review symptom acuity and duration of past episodes of depression	
2. Ensure safety	Choose appropriate treatment venue (e.g., acutely depressed patients may require hospitalization) Monitor suicidality Initiate medical workup as clinically necessary to rule out life-threatening conditions and common causal factors Taper and eliminate if possible use of substances with known depressogenic effects (e.g., sedatives, antihypertensives, steroids, substances of abuse).	
3. Determine the most appropriate regimen for acute treatment from the menu of reasonable choices	Determine treatment priority: tolerability vs. immediate efficacy Review indications for sequential care and urgent care and capacity to maintain acceptable safety within the resources available in the therapeutic venue	
4. Initiate/optimize a treatment plan with bimodal (antidepressant and antimanic/prophylactic) properties	Sequential Care	Urgent Care
	Offer monotherapy treatment with agents that have bimodal activity: lamotrigine, lithium, valproate, olanzapine, quetiapine	Offer ECT or combination treatment with lamotrigine, lithium, valproate, olanzapine, or another agent with proven antimanic or prophylactic activity and an agent with proven efficacy for bipolar depression
5. Determine need for antipsychotic medication	Review indications for antipsychotic medication	Consider conventional antipsychotic agents
6. Consider psychosocial intervention with evidence of acute efficacy	Determine capacity to participate in cognitive-behavioral therapy or another therapy focused on amelioration of acute symptoms	
7. Offer treatment for comorbid conditions	Encourage abstinence, target anxiety symptoms	
8. Determine indication for adjunctive use of agents proven efficacious for unipolar depression	Review antidepressant menu of reasonable choices	
9. Determine indication for ECT	Offer as an option at any time, or When $\geq 2$ adequate trials with agents of known efficacy have proven ineffective, or When unable to tolerate adequate pharmacologic treatment	
10. Determine appropriate follow-up interval	Schedule follow-up	
11. Determine quantity of medication to be dispensed	Review potential for overdose, drug interactions, safety in overdose, and alternatives for dispensing medication	
12. Consider addition of maintenance phase treatments to the acute regimen	See relapse prevention pathway	
13. Determine whether the trial has reached a therapeutic endpoint	Titrate dose to achieve recovery, or declare treatment intolerable or ineffective	
14. Evaluate continuation in pathway	Exit if patient meets criteria for mania, hypomania, mixed, or recovered	

<sup>a</sup>Adapted from Sachs.<sup>12</sup>

Abbreviation: ECT = electroconvulsive therapy.

hazarding if the antidepressant would help the patient recover sooner. However, when looking at recovery times, there was only a slight difference between the 2 treatment groups (antidepressant group = 45 days; no antidepressant group = 49 days).

### Treatment-Emergent Affective Switches

The low rate of treatment-emergent switches to mania, hypomania, or mixed episodes found by double-blind, placebo-controlled trials<sup>7-9,11,15,17</sup> can be reassuring. Treatment-emergent affective switch occurred at rates between 0% (paroxetine)<sup>11</sup> and 50% (desipramine),<sup>17</sup> although most switch rates for active treatments were less

than 10%. Switches occurred in between 2%<sup>11</sup> and 7%<sup>8</sup> of placebo-treated subjects. However, Dr. Sachs portrayed these rates as uncharacteristic of actual treatment scenarios due to the need for ethically acceptable methodology. In these double-blind, controlled trials, rates of mania appear low because subjects routinely discontinue treatment when they experience symptoms of mood elevation consistent with impending mania or hypomania, but short of the full criteria for an episode.

To get an alternate view of treatment-emergent affective switches, Dr. Sachs presented the quasi-experimental data collected at baseline by the STEP-BD. Truman and col-

leagues<sup>18</sup> reported an average treatment-emergent affective switch rate of 37% for the first 500 patients enrolling in the STEP-BD trial.

### Novel Therapeutics

Dr. Sachs recounted the novel approaches that have been used as therapy for bipolar depression, including stimulants, sleep deprivation, phototherapy, rapid transcranial magnetic stimulation, omega-3 fatty acids, and echoplanar magnetic resonance spectroscopic imaging. Small investigations into these therapies might show them to be promising, but, despite their innovation, clinicians should always use caution when prescribing unproven treatments.

## The STEP-BD Approach to Managing Bipolar Depression

To assist clinicians in making the best treatment choices for patients with bipolar depression, STEP-BD offers a disease management program that integrates standardized assessments of treatments and the actual management of patients' individualized treatment.<sup>4</sup>

When making any critical decision about patient treatment, clinicians should first generate a menu of possible treatment choices based on 2 types of data, clinical evidence about the treatments and individual factors including the patient's past response and tolerance. The clinician should then attempt to engage the patient in education about the treatment options and negotiate with him or her about the choice of treatment intervention. Then, the intervention is made, and the results are measured. Follow-up assessment should be conducted in an iterative fashion, allowing the clinician to evaluate whether or not the treatment is appropriate and effective for the patient.

The first strategic decision that a clinician must make is about whether the patient requires sequential care or urgent care. Sequential care involves choosing the treatment option that appears most benign and reasonable. For example, this care approach would be appropriate for outpatients who are mildly or moderately depressed, and it would include starting monotherapy with agents that have bimodal activity (lamotrigine, lithium, valproate, olanzapine, or quetiapine) at a low dose with slow titration. Urgent care is needed for those patients who are in life-threatening episodes, such as bipolar depressed patients who are psychotic or acutely suicidal. Patients receiving urgent care may need electroconvulsive therapy and/or combination pharmacotherapy with a proven anti-manic or prophylactic agent and an agent with bipolar depression efficacy. Urgent care usually requires an aggressive dosing strategy. The complete STEP-BD treatment pathway may be found in Table 3.<sup>12</sup>

## Conclusion

Dr. Sachs affirmed that effective bipolar depression treatment generally requires the use of an agent with robust results for bipolar depression (lamotrigine, olanzapine, quetiapine, or olanzapine/fluoxetine combination).<sup>7-9</sup> Unfortunately, there is no robust evidence to support treatment with standard antidepressants, some of which are associated with treatment-emergent affective switch.<sup>6</sup> The treatment pathway produced by STEP-BD is presented as a useful treatment management schematic that can assist clinicians in providing effective care for patients with bipolar depression.

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## Long-Term Treatment

Since maintenance treatment of bipolar disorder is complicated by the need for care even during the times in which a patient is not in a depressive, manic, or hypomanic episode, being in a treatment relationship is the primary predictor of long-term success for patients with bipolar disorder, reported Charles L. Bowden, M.D. Patients in

long-term treatment, even inadequate treatment, have fewer adverse outcomes than patients who are not involved in some sort of treatment.<sup>1</sup> According to a research report by Angst et al.,<sup>1</sup> treated patients experience a reduction in suicidal as well as nonsuicidal mortality. In addition to increased patient mortality, lack of long-term

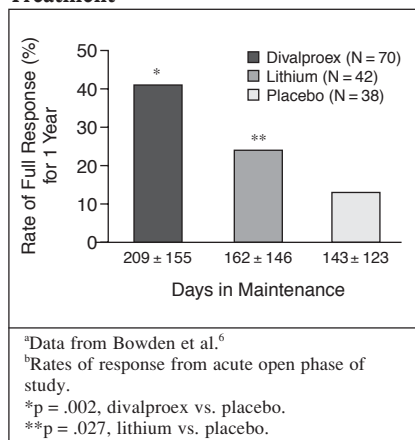
treatment is associated with increased cost per patient, particularly due to higher rates of hospitalization and emergency care.<sup>2</sup> A study<sup>3</sup> comparing patients taking mood stabilizers with patients who had stopped taking them found that those not taking mood stabilizers had a higher rate of hospitalization and an almost 3 times higher rate of attempted suicide. Dr. Bowden attributed these differences in mortality, cost, and adverse outcomes to the tendency of treatment, including pharmacologic treatment, psychoeducation, and the overarching relationship that a patient has with a clinical professional, to reduce the likelihood of full episodes.

Participation in long-term care is necessary in achieving the primary goal of bipolar disorder treatment: functional recovery. A study by Keck and colleagues<sup>4</sup> examined the 12-month outcome of patients with bipolar disorder following hospitalization for manic or mixed episodes and found that, while syndromic recovery was reached by 45% of the patients, only 28% achieved symptomatic recovery and even fewer (20%) attained functional recovery. Functional improvement was generally found to occur only after syndromic and symptomatic resolution, and syndromic recovery was usually attained prior to either of the other types of recovery. Therefore, Dr. Bowden stated, the clinician aiming for functional recovery in a patient with bipolar disorder must assist that patient in achieving and maintaining syndromal and symptomatic recovery.

### Transition From Acute to Maintenance Treatment

After patients with bipolar disorder recover from an episode, in the acute phase of their treatment, they transition into long-term maintenance care. Dr. Bowden illustrated the first few months of a patient's maintenance care as crucial in achieving functional recovery. During the first months of syndromal recovery, dosages of medication that were essential in acute care but were poorly tolerated should be

**Figure 3. Divalproex and Lithium Treatment<sup>a,b</sup>**



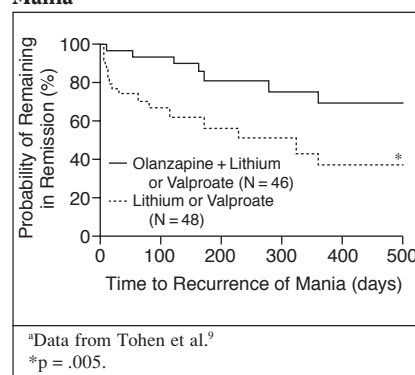
adjusted for tolerability. When a patient is sufficiently coping with everyday living and working conditions, poorly tolerated and nonessential medications should be gradually tapered. If symptoms or functioning begin to worsen, these medications should be restarted.

### Pharmacotherapy Maintenance Treatment

In discussing the need for long-term pharmacologic treatment, Dr. Bowden cited the Expert Consensus Guidelines<sup>5</sup> on the use of mood stabilizers and atypical antipsychotics in patients with bipolar disorder. According to the guidelines, appropriate mood stabilizer treatment should continue indefinitely after response; treatment with atypical antipsychotics should be continued for 20 weeks after response.

Dr. Bowden remarked on the surprisingly little evidence supporting the use of the same medications in maintenance treatment that were successful in acute episode treatment. Divalproex was shown to be more successful than lithium in long-term prophylaxis in a randomized, double-blind, controlled 12-month trial<sup>6</sup> comparing divalproex, lithium, and placebo (Figure 3).<sup>6</sup> Additionally, lithium-treated patients had a 13% higher rate of intolerance or noncompliance. Two 18-month studies<sup>7,8</sup> found lamotrigine and lithium each superior to placebo in preventing

**Figure 4. Olanzapine + Lithium or Valproate Maintenance Treatment of Mania<sup>a</sup>**



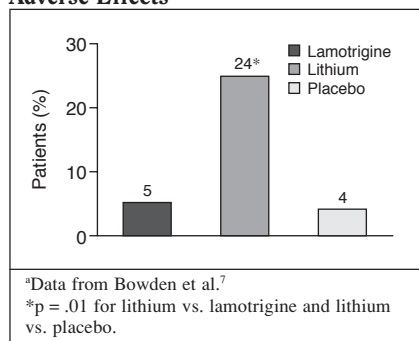
relapse or recurrence of mood episodes. Lamotrigine was more effective than lithium in the prophylaxis of depression, whether the patient's most recent episode was manic or depressive. Conversely, lithium was more effective than lamotrigine in the prophylaxis of mania or hypomania, while showing no significant advantage over placebo in delaying time to depression.

In another 18-month trial, the addition of the atypical antipsychotic olanzapine to lithium or valproate treatment was shown to be effective in prolonging time until symptomatic relapse versus the mood stabilizers alone (median time to relapse: combination therapy 163 days, monotherapy 42 days; p = .023).<sup>9</sup> However, a significant difference in time to syndromic relapse was not shown (median time to relapse: combination therapy 94 days, monotherapy 40.5 days; p = .742). Olanzapine co-therapy was particularly effective in preventing mania recurrence following mania remission (Figure 4).<sup>9</sup>

Selective serotonin reuptake inhibitor (SSRI) co-therapy may also be useful in the maintenance treatment of bipolar disorder to prevent breakthrough depression. In a study by Gyulai et al.,<sup>10</sup> patients who recovered from an acute manic episode within 3 months were randomized to maintenance treatment with divalproex, lithium, or placebo, and those who became depressed were allowed to have SSRI (paroxetine or sertraline) co-therapy. For pa-



**Figure 5. Tolerability of Lamotrigine vs. Lithium: Early Termination due to Adverse Effects<sup>a</sup>**



tients taking SSRIs and placebo (N = 20), 45% discontinued the study prematurely due to worsening depression. Early discontinuation for depression was lower in subjects taking SSRIs and lithium (approximately 30%) and SSRIs and divalproex (10%). SSRI monotherapy for bipolar breakthrough depression does not seem to be an effective treatment; however, co-therapy with mood stabilizers does show some ability to manage depression and improve outcomes.

### Tolerability

Since treatment noncompliance is a serious issue in bipolar disorder, Dr. Bowden stressed the importance of the tolerability of pharmacologic treatment, stating that clinicians and researchers should pay equal attention in their statistical analyses to tolerability as to efficacy.

Comparisons<sup>6,10</sup> of divalproex and lithium show a higher rate of study withdrawal for lithium than for divalproex, which may often be attributable to adverse effects. However, adverse effects were recorded for both medications. Bowden et al.<sup>6</sup> found that divalproex-treated patients had a higher incidence of sedation, infection, and tinnitus than those treated with lithium, while lithium-treated patients had a higher incidence of polyuria and thirst than those taking divalproex. Weight gain was significantly higher in the divalproex group than in placebo, and tremor was more common with both medications than with placebo.

Lithium was tolerated less well than lamotrigine in a study by Bowden et al.<sup>7</sup> Lamotrigine-treated and placebo-treated patients had a significantly lower rate of discontinuation due to adverse events than lithium-treated patients (Figure 5).<sup>7</sup> The adverse events occurring in both active treatment groups included headache, rash, diarrhea, nausea, insomnia, and others. However, most of these side effects were considered mild or moderate and were resolved without sequelae. The most common adverse event was headache, which occurred more among lamotrigine-treated patients than lithium-treated patients. The incidence of diarrhea was significantly higher in the lithium group than in the lamotrigine group. Overall, lamotrigine was shown to be a well-tolerated medication for the maintenance treatment of bipolar disorder.

Since weight gain has been increasingly viewed as a risk factor for metabolic syndrome, clinicians may need to consider the side effect of weight gain when prescribing medications for long-term treatment of bipolar disorder. Olanzapine and mood stabilizer co-therapy is associated with significantly more weight gain than mood stabilizer monotherapy.<sup>9</sup> After an 18-month study, patients treated with olanzapine and mood stabilizer co-therapy had gained an average of 2 kg, but the mean weight change of patients on mood stabilizer monotherapy was a loss of 1.82 kg. A comparison<sup>11</sup> of lamotrigine and lithium treatment showed a significantly higher weight gain in obese patients with lithium than with lamotrigine. Over the first year of treatment, patients taking lithium gained an average of 3.3 kg, while patients taking lamotrigine lost an average of 2.96 kg.

### Combination Therapy

The role of combination treatments extends beyond pharmacologic co-therapy; Dr. Bowden endorsed the augmentation of mood stabilizing medication regimens with various forms of psychoeducation and psychotherapy.

Several long-term, well-defined studies<sup>12-14</sup> have shown that these adjunctive therapies can have substantial benefit in the maintenance treatment of bipolar disorder.

### Conclusion

Clinicians who are working with patients to manage bipolar disorder during long-term care should have an illness-focused approach to treatment instead of one that focuses only on the individual episodes. In an effort to help a patient predict and prevent new episodes, it is important to help the patient understand destabilizing factors that may lead to relapse and prodromes that may indicate the patient is on the path toward an episode recurrence. Illustrating these destabilizing factors and prodromes often requires the clinician to be empathetic but direct in helping patients recognize subtle degrees of self-denial or under-recognition of the seriousness or scope of their illness. Clinicians should work with family members in this area whenever possible. Aiming beyond limited improvement and resolution of full episodes, the ultimate goal for clinician and patient should be total recovery and responsible participation in long-term treatment.

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risk of dropping out of therapy is substantial in bipolar disorder, psychosocial interventions focus on maintaining and strengthening a treatment alliance between patients and caregivers.

### Psychosocial Intervention for Bipolar Disorder

There are 4 types of psychosocial interventions that have been examined and have proven useful in treating bipolar disorder. These include psychoeducation, cognitive-behavioral therapy, interpersonal and social rhythm therapy, and family-focused therapy.

**Psychoeducation.** In recent years, psychoeducation for bipolar disorder has been studied in several single-blind, randomized trials. In a study<sup>12</sup> published in 1999, Perry and colleagues examined the use of a relatively brief psychoeducational intervention in 69 bipolar patients who had relapsed within the previous year. While the control group received routine care, the treatment group received routine care and 7 to 12 individual psychoeducation sessions focused on strengthening the therapeutic relationship, identifying and forestalling relapse, and improving medication adherence. At the end of the 18-month study, the psychoeducation group had a significantly lower rate of relapse to mania than the control group (27% vs. 57%). Patients participating in psychoeducation also experienced a lower rate of depressive relapse, but it was not significantly different from that of the control group.

Colom and colleagues<sup>13</sup> conducted a larger randomized, parallel group, single-blind study. The 120 subjects were bipolar patients who had been in remission for at least 6 months. After being randomized into 2 groups of equal number, the treatment group participated in 21 psychoeducational group sessions and received standard care while the control group participated in 21 nonstructured group sessions and received standard care. This trial showed that psychoeducational

## Psychosocial Management

Although bipolar disorder has long been considered one of the most biological of psychiatric disorders and the most biological of the mood disorders, research investigating the role of psychotherapy in treating bipolar disorder has recently increased, according to Michael E. Thase, M.D. Dr. Thase attributed this growth in research to 4 confluent forces or new understandings that have bolstered this use of psychotherapy.

First, the ultimately limited efficacy of standard pharmacologic treatment has prompted clinicians and researchers to look for new potentially effective adjunctive therapies. Second, medication adherence is directly linked to long-term outcomes in bipolar disorder treatment, and patients' feelings and beliefs about their disorder and its treatment greatly affect adherence.<sup>1–4</sup> Since psychosocial interventions influence these thoughts and feelings, they may be used to increase medication adherence and, therefore, to improve outcomes. Third, the established and efficacious use of various forms of psychotherapy in treating schizophrenia<sup>5–7</sup> and evidence of benefit from psychosocial interventions in unipolar depression<sup>8</sup> have helped to support the use of psychosocial treatment in bipolar disorder.

Perhaps the most powerful rationale behind this heightened interest in psychotherapy is the recognition that psychosocial risk factors contribute to the course of bipolar illness.<sup>9–11</sup> These risk factors include a patient's life stress and adverse life events as well as his or her level of social support, and acknowledging the importance of these risk factors has opened the door to adjunctive psychosocial therapies that can address them.

Because people with bipolar disorder experience more successful treatment outcomes when they are active participants in the care of their disorder, the goal of all psychosocial interventions for bipolar disorder is the engagement of the patient in a collaborative, problem-solving process that includes learning about the illness and its management. Psychosocial therapies are primarily concerned with relapse prevention, so all the therapies teach patients to recognize the signs of impending relapse and what can be done to forestall relapses. Patients are educated about the various ways to ask for help. The importance of treatment adherence is stressed and patients are encouraged to collaborate and cooperate with their clinicians in managing their pharmacologic treatment, including lessening side effects. Since the

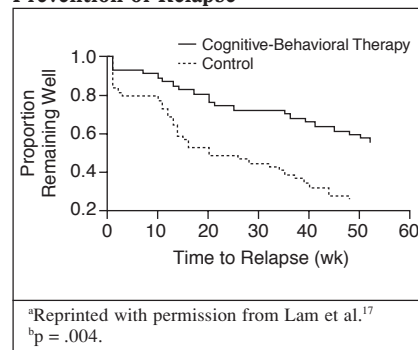
intervention was associated with reduced relapse. After 2 years of follow-up, the control group had a relapse rate of 92%, while the treatment group had a relapse rate of 67%. Both groups of subjects were high-risk patients, so, despite a high relapse rate, psychoeducation did significantly reduce relapse compared with the control treatment.

Dr. Thase described 2 additional psychoeducation studies that are currently in process. Bauer and McBride<sup>14</sup> have created the Life Goals Program and are testing it at Veterans Administration Medical Centers across the United States. The Life Goals Program<sup>14</sup> is a structured, manual-based group psychotherapy program for bipolar disorder that enrolls a fixed cohort of 5 to 6 patients under the direction of a therapist. The program is divided into 2 phases. In the first phase, patients participate in 5 weekly psychoeducational sessions that include an overview of the illness and its treatment and sessions focusing on depression, mania, and hypomania. During the second phase, the patients identify and work toward one or more behavioral life goals.

Simon and colleagues<sup>15</sup> are conducting another psychoeducation study in the Puget Sound Managed Care Network. In addition to usual care, this bipolar disorder management program includes the development of a collaborative treatment plan, the delivery of a structured psychoeducational group program (Life Goals<sup>14</sup>) by a nurse, monthly telephone monitoring by an experienced psychiatric nurse, and feedback to the care providers. This program and the Life Goals program are less intensive interventions and may prove to be affordable and practical applications of psychoeducation.

**Cognitive-behavioral therapy.** Borrowed from the realm of depression treatment, cognitive-behavioral therapy (CBT) for bipolar disorder was originally advanced in a book<sup>16</sup> by Basco and Rush in 1996. CBT for bipolar disorder helps patients identify and correct negative thoughts through using cognitive-restructuring exer-

**Figure 6. Cognitive-Behavioral Therapy Prevention of Relapse<sup>a,b</sup>**



cises, self-monitoring diaries, daily homework assignments, and step-wise behavioral assignments.

Lam and colleagues<sup>17</sup> tested CBT for bipolar disorder in a study published in 2003 and found that CBT substantially reduced the rate of relapse. Across a 12-month protocol, 75% of the control group relapsed compared with only 44% of the group participating in CBT (Figure 6).<sup>17</sup> In this study, CBT was most effective in reducing the number of depressive episodes.

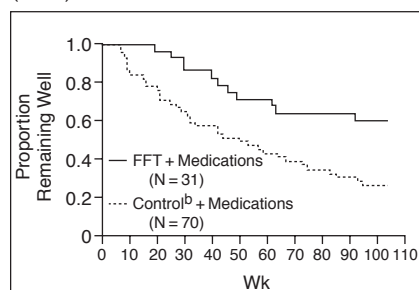
More recently, CBT has been studied by Scott and colleagues<sup>18</sup>; this study did not find that CBT had a significant effect in patients with bipolar disorder. However, a follow-up analysis of the study revealed a relationship between the patients' number of lifetime episodes and how they responded to CBT intervention. Patients with many episodes tended to respond better to the control conditions than to CBT, while patients with relatively few episodes had a better response to the CBT intervention. Dr. Thase explained that the results of this study indicate that the relationship between response in bipolar disorder and psychosocial therapies may be more complex than generally assumed. The results also suggest that this type of focused psychosocial intervention may be most effective early in the lifetime course of a patient's bipolar disorder.<sup>18</sup>

**Interpersonal and Social Rhythm Therapy.** Interpersonal and Social Rhythm Therapy (IPSRT)<sup>19</sup> is the con-

vergence of 2 types of psychosocial interventions—a simple, practical form of psychotherapy that helps patients to identify areas of interpersonal conflict and either resolve them or come to terms with them, and behavioral strategies that help patients to regulate their daily routines based on the relationship between social rhythms and mood stability.<sup>20</sup> IPSRT incorporates psychoeducation, illness management, development of regular daily rhythms, identification of potential daily rhythm interferences (specifically looking at interpersonal triggers that may cause rhythm disruption), and assistance in dealing with the grief associated with the loss of the “healthy” self.<sup>19</sup>

A large trial<sup>21</sup> of IPSRT was conducted by Frank and colleagues at the University of Pittsburgh. In this trial, patients in acute episodes (manic, depressed, or mixed) were randomized into 2 treatment groups. During the acute treatment phase, control patients received pharmacologic treatment and 12 sessions of intensive clinical management, while the treatment group received pharmacologic treatment and IPSRT. The acute treatment phase continued until patients had completed 4 weeks of stable remission of both depression and mania. The 126 patients who achieved stable remission were then randomized into 2 treatment groups for a 2-year maintenance phase—intensive clinical management or IPSRT. Therefore, 4 treatment sequences were possible: IPSRT followed by intensive clinical management, IPSRT for both phases, intensive clinical management followed by IPSRT, or intensive clinical management for both phases. The 2 treatment strategies did not result in different times to stabilization. Acute IPSRT led to a longer time before a new affective episode emerged, no matter the maintenance treatment.

**Family-focused therapy.** Since people with bipolar disorder tend to have substantial problems with their families and are particularly vulnerable to the loss of positive family social support, psychosocial therapy that

**Figure 7. Family-Focused Therapy (FFT): Time to Recurrence<sup>a</sup>**

<sup>a</sup>Reprinted with permission from Miklowitz et al.<sup>22</sup>

<sup>b</sup>Crisis management is a less intensive psychoeducational intervention.

specifically addresses these problems has proven effective in reducing relapse rates among patients.<sup>22</sup> In the family-focused therapy studies by Miklowitz and colleagues,<sup>22,23</sup> patients worked with their spouses, romantic partners, or their parents and siblings if they still lived with their family of origin. Patients and family members participated in 21 one-hour sessions that included psychoeducation, communication-enhancement training, and problem-solving skills training. Two studies<sup>22,23</sup> of family-focused therapy found that it was significantly associated with relapse prevention effects. In a randomized, controlled trial of 101 patients with bipolar disorder, 53% of patients participating in family-focused therapy avoided relapse during the 2-year followup compared with only 17% of the control group. Family-focused therapy was also significantly associated with longer time to recurrence (Figure 7).<sup>22</sup>

### Conclusion

Dr. Thase concluded that these 4 types of psychosocial intervention have been documented as having a positive impact on the long-term course of bipolar disorder. Although none of the interventions seem to hasten recovery from acute episodes, they

do prove effective in relapse prevention. Dr. Thase asserted the value of psychosocial therapies as meaningful and cost-effective approaches to improvement for patients with bipolar disorder who have not been able to achieve or maintain recovery with the more conventional “medical model” of pharmacologic treatment.

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**Drug names:** aripiprazole (Abilify), bupropion (Wellbutrin and others), carbamazepine (Carbatrol, Equetrol, and others), chlorpromazine (Thorazine, Sonazine, and others), desipramine (Norpramin and others), divalproex (Depakote), fluoxetine (Prozac and others), gabapentin (Neurontin and others), haloperidol (Haldol and others), imipramine (Tofranil and others), lamotrigine (Lamictal), levetiracetam (Keppra), lithium (Eskalith, Lithobid, and others), olanzapine (Zyprexa), olanzapine/fluoxetine combination (Symbyax), oxcarbazepine (Trileptal), paroxetine (Paxil, Pexeva, and others), quetiapine (Seroquel), risperidone (Risperdal), sertraline (Zoloft), topiramate (Topamax), tranylcypromine (Parnate), venlafaxine (Effexor), ziprasidone (Geodon), zonisamide (Zonegran).

**Disclosure of off-label usage:** The chair has determined that, to the best of his knowledge, no investigational information about pharmaceutical agents that is outside U.S. Food and Drug Administration–approved labeling has been presented in this activity.

For the CME Posttest for this article, see pages 1649–1651.