International Consensus Group on Bipolar I Depression Treatment Guidelines

This ACADEMIC HIGHLIGHTS section of The Journal of Clinical Psychiatry *presents the highlights of the meeting "International Consensus Group on Bipolar I Depression Treatment Guidelines," held December 4, 2003, in New York, N.Y.*

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This ACADEMIC HIGHLIGHTS was supported by an unrestricted educational grant from GlaxoSmithKline.

Financial disclosure appears at the end of this article.

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Dr. Calabrese began the meeting by saying that in the management of bipolar disorder the guidelines available for treating mania are fairly standard worldwide. However, the guidelines for treating bipolar depression vary, sometimes substantially, from country to country. Therefore, the primary aim of the consensus group was to discuss the treatment of bipolar I depression across different countries and develop a consensus on international treatment guidelines for this phase of the illness. The group sought to formulate its recommendations on the basis of the available clinical evidence, rather than relying on expert opinion as is the case with some guidelines, given the numerous agents being studied for bipolar depression in well-designed clinical trials.

Barriers to Effective Treatment for Bipolar I Depression

Unrecognized Bipolar I Depression

During their discussion, the group recognized several impediments to effective treatment for bipolar I depression and to the adoption of treatment guidelines. One reason patients with bipolar I depression do not get effective care is that this diagnosis has long been overlooked. In the study of bipolar disorder, mania appears to have received more attention, so that, according to Dr. Kasper, only now is bipolar depression emerging as an area of interest. Consequently, clinicians tend to recognize mania more readily than bipolar depression. Drs. Young and Tajima said that in their respective countries, Britain and Japan, bipolar depression is generally underdiagnosed or misdiagnosed as unipolar depression. In Japan, psychiatrists typically concentrate on the prevention of mania, mixed mania, or manic relapse, which means treatments for mania have recently dominated the market there.

Antidepressant Therapy in Bipolar I Depression

Since manic episodes have been most often studied in bipolar disorder, recognition and treatment of depressive episodes has lagged behind. As Dr. Yatham pointed out, the advances in treatment for bipolar depression have been fairly recent, which meant that, until a few years ago, little evidence existed about what agents would treat bipolar depression. Therefore, clinicians treated depressive symptoms with what they knew worked—antidepressants—giving little consideration as to whether the depression was unipolar or bipolar. Although medications to treat specifically bipolar depression are today more readily available, antidepressant monotherapy, according to the consensus group, continues to be the most common treatment for bipolar I depression in their respective countries, despite little to no clinical evidence proving its efficacy as a treatment. For example, in a survey completed by over 3000

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Table 1. Blinded, Controlled Trials of Long-Term Antidepressant Treatment in Bipolar I Disorder[a]

Study	N	Treatments	Duration (mo)	Outcome	Results
Prien et al, 1973[2]	44	Li vs IMI vs PBO	Up to 24	Hospitalized or new treatment	Depression: Li > IMI = PBO
Wehr and Goodwin, 1979[3]	5	Li vs Li + DMI	27 (mean)	Nurse ratings	Depression: Li + DMI > Li Switch and cycling rate: Li + DMI >> Li
Quitkin et al, 1981[4]	75	Li vs Li + IMI	19 (mean)	RDC episodes	Depression: Li = Li + IMI Mania: Li + IMI > Li (women)
Prien et al, 1984[5]	117	Li vs Li + IMI vs IMI	Up to 24	RDC episodes	Depression: Li = Li + IMI = IMI Mania: Li = Li + IMI > IMI
Sachs et al, 1994[6]	15	Li + BUP vs Li + DMI	Up to 12	DSM-III-R episodes	Depression: Li + BUP = Li + DMI Mania: Li + BUP > Li + DMI

[a]Adapted with permission from Ghaemi et al.[1]
Abbreviations: BUP = bupropion, DMI = desipramine HCl, IMI = imipramine HCl, Li = lithium carbonate, PBO = placebo, RDC = Research Diagnostic Criteria.
Symbols: > = more effective than, >> = much more effective than.

Table 2. Commonly Held Misbeliefs About Bipolar Depression Treatment Not Supported by Research Evidence

Bipolar disorder is not a lifelong illness, so treatment of only acute episodes is necessary
Antidepressant monotherapy should be first-line treatment, with mood stabilizer augmentation if manic symptoms appear
An antidepressant–mood stabilizer combination has a more rapid onset of action than a mood stabilizer alone
Recent episode frequency is not important in treatment selection

individuals in the United States, antidepressant monotherapy was the most frequently received treatment as reported by people who screened positive for bipolar disorder according to the Mood Disorder Questionnaire (M. A. Frye, M.D., J.R.C., M. Reed, Ph.D., et al., manuscript submitted).

In a review of the literature on long-term antidepressant treatment in bipolar disorder, Ghaemi et al.[1] found studies in this treatment area to be sparse—only 5 blinded, long-term controlled trials[2–6] in bipolar I patients—and to offer inadequate support for the efficacy of antidepressant treatments (Table 1). Rather, what the available data did support was that antidepressants, either alone or in combination with lithium, may induce mania or rapid cycling. A more recent study by Gyulai et al.[7] adds weight to this review by providing randomized, blinded maintenance data that indicate not only is antidepressant monotherapy significantly less effective in preventing breakthrough depression in bipolar disorder than an antidepressant–mood stabilizer combination ($p = .003$), but antidepressant monotherapy also worsens the overall course of the illness.

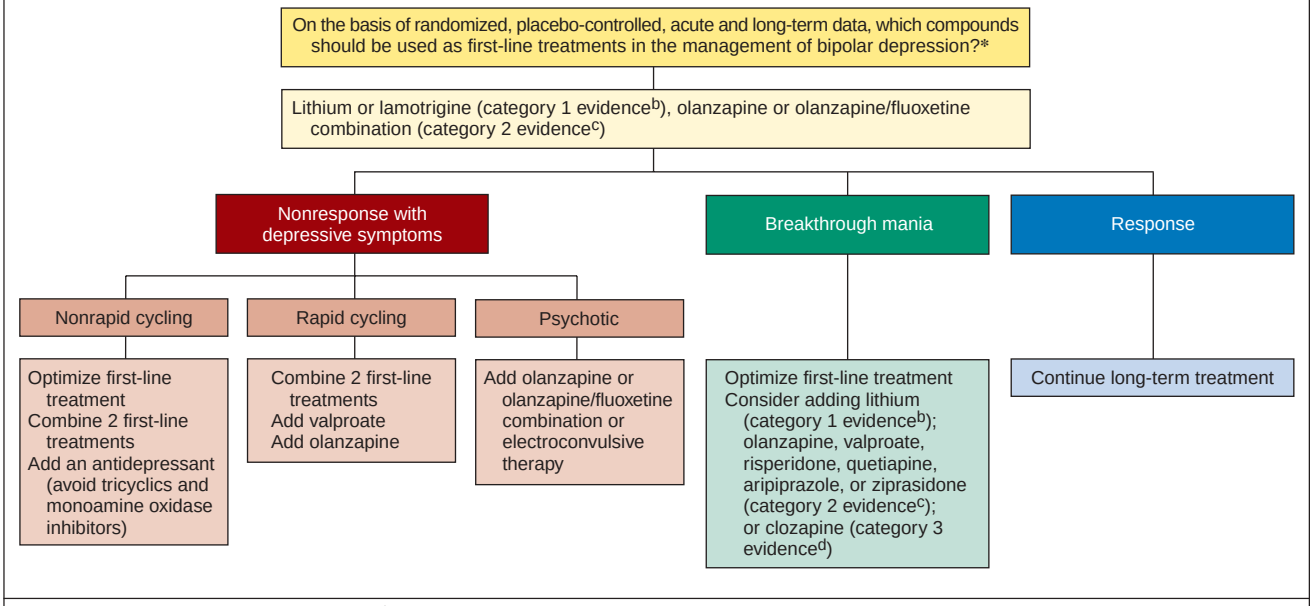
Many treatment guidelines, like those of the American Psychiatric Association,[8] recommend avoiding antidepressant monotherapy for bipolar depression, but the frequent use of these treatments indicates a disconnect between guidelines and clinical practice. Dr. Yatham proposed that clinicians may be more comfortable prescribing antidepressants because, historically, these were the available drugs. Dr. Vieta added that patients themselves may also be another reason for the popular use of antidepressants in bipolar depression. The patients may have been previously treated with antidepressants because they were misdiagnosed and/or they may have experienced a switch to mania or hypomania and found it pleasant. Therefore, some doctors may feel pressure from patients to treat them with antidepressants. Dr. Yatham suggested that if warnings about antidepressants in bipolar disorder are repeated often, clinicians will use more appropriate treatments. He cited the increased use of atypical antipsychotic monotherapy for acute mania in bipolar patients as an example of clinical evidence changing treatment practices: whereas atypical antipsychotic monotherapy for bipolar patients was once unthinkable in Canada, now, with the availability of long-term data, clinicians are beginning to use this drug class as monotherapy.

Misbeliefs About Bipolar I Depression Treatment

In addition to the misconception that antidepressant monotherapy should be a first-line treatment for bipolar I depression, the group identified other commonly held misbeliefs about bipolar depression treatment that have little research evidence to support them (Table 2).

The group agreed that bipolar disorder is a chronic illness that requires lifelong treatment, i.e., clinicians need to treat the disease and not just the presenting episode. The whole illness—rather than simply acute manic or depressive episodes—must be considered to ensure success when making treatment decisions. Dr. Vieta offered that the acute episode must be treated while weighing the long-term treatment outcome, and Dr. Young added that in practice clinicians often continue the acute treatment for a minimum of 6 months after the symptoms have resolved. Dr. Yatham suggested that although the growing recognition that bipolar disorder is a chronic illness should facilitate the use of medication with documented long-term efficacy, asking physicians to look at the efficacy of both acute and long-term treatments will require a paradigm shift. The group concluded that both acute and long-term safety and efficacy data should be considered when selecting first-line treatments for bipolar depression.

Figure 1. International Consensus Guidelines on the Treatment of Bipolar I Depression[a]



[a]Treatment guidelines in which no categories of evidence are given are not supported by category level evidence.
[b]Category 1 evidence = randomized placebo-controlled trial(s) in treatment of acute bipolar depression (or breakthrough mania) and long-term treatment for both poles of illness in both recently depressed and recently manic patients.
[c]Category 2 evidence = randomized placebo-controlled trial(s) in acute phase for which patient is being treated or randomized placebo-controlled trial(s) in long-term treatment from 1 pole of illness that suggest no mood destabilization.
[d]Category 3 evidence = randomized controlled trial(s) in any phase of bipolar disorder treatment.
*The authors reached the consensus that the presence of long-term safety and efficacy data should impact medication selection for the acute treatment of bipolar depression.

Developing Treatment Guidelines

The group decided to prioritize its treatment recommendations on the basis of clinical evidence (Figure 1). Therefore, agents meeting category 1 evidence had to have randomized placebo-controlled trial(s) in the treatment of acute bipolar depression (or breakthrough mania) and in the long-term treatment for both poles of illness in both recently depressed and recently manic patients. Agents meeting category 2 evidence had to have randomized placebo-controlled trial(s) in the acute phase for which the patient is being treated or randomized placebo-controlled trial(s) in the long-term treatment from 1 pole of illness that suggest no mood destabilization. Finally, agents meeting category 3 evidence had to have randomized controlled trial(s) in any phase of bipolar disorder treatment.

First-Line Treatments for the Management of Bipolar I Depression

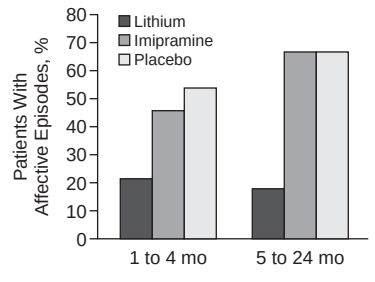
Lithium

The group acknowledged that although many of the studies of lithium in bipolar I depression were poorly designed crossover trials, the number of studies that found lithium to be effective for bipolar depression is too great to ignore. The group's consensus about lithium is echoed in a review by Zornberg and Pope[9] on the use of lithium in acute bipolar depression. These authors concluded that, despite methodologic limitations, the research supported the efficacy of lithium over placebo in the treatment of bipolar depression.

A common study practice in early acute research was to compare acute lithium response in patients with bipolar depression with lithium response in patients with unipolar depression. Goodwin et al.[10] identified depressed patients as bipolar (either I or II, N = 40) or unipolar (N = 12) and gave them lithium for at least 2 weeks followed by placebo for at least 6 days. The outcome measure was the mean depression rating for the 4 days prior to the initiation of lithium treatment compared with the mean depression rating for the last 4 days of lithium treatment. Of the patients who responded to lithium, 40% had a complete remission of symptoms. The difference between the bipolar patients and unipolar patients who had some symptom improvement with lithium treatment was statistically significant ($p < .02$) (80% versus 33%, respectively).

Later, Mendels,[11] in a review of lithium as a depression treatment, reported the results of his study of lithium in 21 moderately-to-severely depressed hospitalized patients (N = 13 for bipolar

Figure 2. Bipolar Patients With Affective Episodes After Acute or Prophylactic Treatment With Lithium, Imipramine, or Placebo[a]



[a]Data from Prien et al.[2] For 1 to 4 months, N = 18 for lithium, N = 13 for imipramine, and N = 13 for placebo. For 5 to 24 months, N = 17 for lithium, N = 9 for imipramine, and N = 9 for placebo.

and N = 8 for unipolar). Placebo was given to the patients for 7 to 15 days; lithium was then titrated to optimal or maximum doses, which were maintained for 21 days. After the lithium treatment, patients were again given placebo for 7 to 22 days. Outcome measures were symptom relief that required no treatment other than lithium and a return to premorbid functioning, as well as several rating scales. Of the 13 patients who improved, 9 were bipolar and 4 were unipolar. From this group of responders, 6 with bipolar depression and 1 with unipolar depression relapsed during placebo treatment. Dr. Young pointed out that a similar relapse outcome had been reported[12] after discontinuation of lithium for mania and warned that abrupt discontinuation of lithium, especially after acute treatment, may make patients' symptoms worse than if they had no treatment at all.

The prophylactic efficacy of lithium in recently depressed bipolar patients has been reported by Prien et al.[2] Patients (N = 122) were admitted to the study after being hospitalized for an acute depressive episode and were diagnosed as bipolar or unipolar on the basis of a history of mania. They were randomly assigned to receive lithium (median dose = 1250 mg/day), imipramine (median dose = 125 mg/day), or placebo and were scheduled to receive this treatment for 2 years. The authors analyzed the episodes that occurred in the first 4 months of prophylactic treatment, which may have been relapse episodes, separately from the episodes that occurred in the remaining 20 months of treatment; in general, however, the number of episodes did not substantially differ across time.

Throughout the study,[2] lithium was significantly more effective than the other treatments in the prevention of depressive or manic episodes in bipolar patients (Figure 2). Further, of the bipolar patients who actually completed the study, 9 taking lithium remained episode-free for the entire 2 years, compared with 2 taking imipramine and 1 taking placebo who remained episode-free. In the last 20 months, among bipolar patients treated with lithium, 12% experienced depressive episodes and 12% had manic episodes. During this same period, depressive episodes occurred in none of the imipramine-treated bipolar patients and 55% of the placebo-treated patients, while manic episodes occurred in 67% in the imipramine group and 33% of the placebo group.

Lamotrigine

In a double-blind placebo-controlled trial, Calabrese and colleagues[13] studied the efficacy of lamotrigine in the acute treatment of bipolar I depression. Patients (N = 195) who were diagnosed with DSM-IV bipolar I disorder and were experiencing a major depressive episode lasting from 2 weeks to 12 months were randomly assigned to lamotrigine, 50 or 200 mg/day, or placebo for 7 weeks. Outcome measures included the Hamilton Rating Scale for Depression (HAM-D), Montgomery-Asberg Depression Rating Scale (MADRS), and Clinical Global Impressions scales for Severity (CGI-S) and Improvement (CGI-I). Lamotrigine was significantly more effective than placebo on most, but not all, outcome measures. Patients receiving 200 mg daily exhibited significant improvement on all efficacy endpoints using both LOCF and observed case analyses, except the LOCF analysis of the 17-item HAM-D and both analyses of the 31-item HAM-D total score. Over 50% of patients given 200 mg daily met response criteria on the 17-item HAM-D, MADRS, and CGI-I. For MADRS and CGI-I, this rate of improvement was significantly higher and nearly twice that observed for those given placebo. Compared with the lamotrigine 200-mg/day group, the lamotrigine 50-mg/day group showed significant efficacy on fewer measures and the proportion of responders was somewhat lower. As early as week 3, lamotrigine-treated patients, who were all given ≤ 50 mg/day for the first 3 weeks, showed significant improvement ($p < .05$) on the HAM-D Item 1, MADRS, CGI-S, and CGI-I. These results demonstrated the efficacy of lamotrigine for the treatment of acute bipolar I depression.

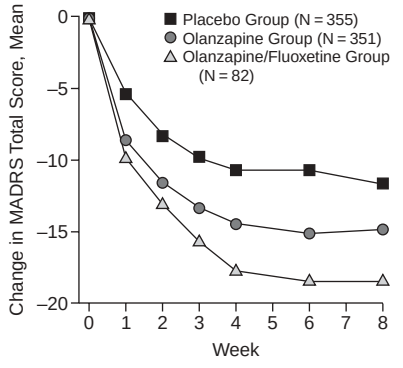
After an 8- to 16-week open-label trial with lamotrigine, patients who met DSM-IV criteria for bipolar I disorder and who were recently depressed were randomly assigned to lamotrigine (50, 200, or 400 mg/day; N = 221), lithium (titrated to serum levels of 0.8–1.1 mEq/L; N = 121), or placebo (N = 121) monotherapy for up to 18 months of maintenance treatment.[14] Time to intervention (e.g., pharmacotherapy or electroconvulsive therapy [ECT]) for any mood episode was the primary outcome measure. At 1 year, almost 60% of patients treated with 200 mg/day of lamotrigine were intervention-free for depressive episodes compared with 45% of patients treated with placebo (Table 3). Overall, lamotrigine was more effective at delaying intervention for depressive episodes than placebo, while lithium was more effective at delaying intervention for manic episodes than placebo. The same results were observed in a separate study[15] of similar design in which bipolar I patients who were recently manic or hypomanic were assigned to lamotrigine (100–400 mg/day, N = 59), lithium (titrated to serum levels of 0.8–1.1 mEq/L, N = 46), or placebo (N = 70) monotherapy for up to 18 months of maintenance treatment.

Table 3. Survival Data for Recently Depressed Bipolar I Disorder Patients Treated With Placebo, Lithium, or Lamotrigine[a]

Intervention for Depression	Number of Events	1 Year, Intervention-Free Rate (%)	95% Confidence Interval	p Value vs Placebo[b]
Placebo (N = 119)	47	45	32, 57	N/A
Lithium (N = 120)	46	46	35, 58	.209
Lamotrigine 50 mg/d (N = 50)	20	49	33, 66	.413
Lamotrigine 200 mg/d (N = 120)	40	58	48, 69	.028
Lamotrigine 400 mg/d (N = 45)	17	54	36, 71	.533

[a]Adapted with permission from Calabrese et al.[14]
[b]Difference in survival distributions between treatments tested using a log-rank test.
Abbreviation: N/A = not applicable.

Figure 3. Mean Change in Montgomery-Asberg Depression Rating Scale (MADRS) Total Scores for Patients Treated With Placebo, Olanzapine, or Olanzapine/Fluoxetine Combination for 8 Weeks[a]



[a]Reprinted with permission from Tohen et al.[16] Randomized patients with insufficient postbaseline visits were not included in this analysis. The change in MADRS scores of patients treated with the active agents was significantly greater than that of patients taking placebo throughout the 8 weeks ($p < .001$). The change in MADRS scores of patients treated with olanzapine/fluoxetine combination was significantly greater than that of patients taking olanzapine in the final 4 weeks of the study ($p < .02$).

Olanzapine and Olanzapine/Fluoxetine Combination

Evidence from a recently published randomized placebo-controlled 8-week trial[16] showed that olanzapine and the olanzapine/fluoxetine combination were effective treatments for bipolar I depression. Patients meeting DSM-IV criteria for bipolar I depression, who also had a score of at least 20 on the MADRS, were randomly assigned to placebo (N = 377); 5 to 20 mg/day of olanzapine (N = 370); or 6 and 25, 6 and 50, or 12 and 50 mg/day of olanzapine/fluoxetine combination (N = 86). Throughout the study, olanzapine and olanzapine/fluoxetine combination were statistically superior to placebo in the treatment of depressive symptoms ($p < .001$) (Figure 3). At week 8, MADRS scores had dropped 15 points from baseline for patients taking olanzapine and 18.5 points for patients taking olanzapine/fluoxetine combination but only 11.9 points for patients taking placebo. The olanzapine/fluoxetine combination–treated group had statistically significantly higher rates of response and remission than the olanzapine-treated and placebo-treated groups, while the olanzapine-treated group had statistically significantly higher rates of response and remission than the placebo-treated group. The rates of treatment-emergent mania were low for all 3 treatment groups.

Although double-blind evidence is not yet available for the effectiveness of olanzapine and the olanzapine/fluoxetine combination as maintenance treatments for bipolar I depression, open-label data[17] are promising. Patients (N = 192) with bipolar depression in remission after 8 weeks of randomized, double-blind treatment with olanzapine, olanzapine/fluoxetine combination, or placebo were switched from their acute treatment to olanzapine. If necessary, patients were then switched to olanzapine/fluoxetine combination after 1 week of olanzapine therapy. Approximately 60% of patients remained in remission over the 6-month maintenance period, but to which treatment group most of these patients belonged was not reported.

Treatment Nonresponse With Depressive Symptoms

Nonrapid Cycling

The group agreed that optimizing treatment should be clinicians' first response for patients with bipolar I depression who have not responded to treatment and have nonrapid cycling. Optimization includes ensuring that the patient has received an adequate dose of the agent for an adequate period of time. If dose and duration appear to be acceptable, clinicians should query patients about compliance, checking serum drug levels if needed. Clinicians may also find it necessary to treat any comorbid conditions and look for psychosocial or personality problems.

If optimization is unsuccessful, the group recommended combining 2 first-line treatments for bipolar patients with nonrapid cycling, although they acknowledged that to date there is no category 1 or 2 evidence to support the recommendation. The other option when optimization fails is to add an antidepressant. The group discussed which antidepressants are most likely to cause manic switches and determined that the available evidence suggests tricyclic antidepressants (TCAs) and monoamine oxidase inhibitors (MAOIs) are most known to induce mania. For example, Peet[18] pooled data to compare the rate of manic switches in bipolar patients treated with selective serotonin reuptake inhibitors (SSRIs) with the rate of patients treated with TCAs or placebo. The switch rate was about the same for patients treated with SSRIs or placebo, but the difference in the switch rates for patients treated with SSRIs or TCAs was statistically significant, with the percent who switched being 3.7% for SSRIs and 11.2% for TCAs. In a later review, Peet and Peters[19] indicated MAOIs were also known to induce mania in bipolar patients. In their review of the literature, Wehr and Goodwin[20] reached a similar conclusion about mania induced by TCAs and MAOIs.

Of relevance to the treatment option of adding an antidepressant to a first-line treatment, the group concurred, was a recent article by Altshuler et al.[21] on the frequency of depressive relapse in a highly enriched sample of bipolar patients who were selected for response and toleration of antidepressant treatment and then who did or did not stop taking the antidepressant. In the study, bipolar patients (N = 84) whose depression remitted after an antidepressant (e.g., SSRI, bupropion, venlafaxine, TCA, or MAOI) was added to a mood stabilizer were followed for 1 year. During the follow-up period, 70% of patients who stopped antidepressant treatment within 6 months of remitting experienced a depressive relapse compared with only 24% of patients who continued to take antidepressants throughout the year after remission. On the basis of these results, Altshuler et al. concluded that, in those patients who respond to and tolerate antidepressant treatment, continuing antidepressant treatment for at least a year after remission from a depressive episode may decrease the likelihood of future depressive episodes. However, none of the patients with a recent history of rapid cycling responded to treatment with antidepressants (L. L. Altshuler, M.D.; J.R.C., oral communication).

Rapid Cycling

Since the DSM-IV was published, rapid cycling has been recognized as a distinct course modifier for bipolar disorder, but most of the group members opined that rapid cycling continues to be unrecognized by many clinicians as a serious issue that could affect treatment selection. Clinicians may not ask their patients about episode frequency because they do not consider it an important factor in the management of bipolar disorder (see Table 2).

At one time, rapid cycling was thought to be a specific predictor of nonresponse to treatment, but recent evidence suggests that this illness variant is actually a nonspecific predictor of severity of illness.[22] Therefore, for patients who are not responding to treatment and have rapid cycling, the group recommended combining 2 first-line treatments.

To test the hypothesis that rapid cycling was a predictor of nonresponse to lithium and positive response to divalproex, Calabrese and colleagues[23] conducted a randomized controlled long-term maintenance trial. A 20-month, double-blind, parallel group comparison was carried out in recently hypomanic/manic outpatients who experienced a persistent bimodal response to combined treatment with lithium and divalproex. Sixty patients were to be randomized to either lithium or divalproex monotherapy in a balanced design after stratifying for bipolar type I and II. The rate of relapse into depression was 34% with lithium and 29% with divalproex. The rate of relapse into hypomania/mania was 22% for both lithium and divalproex. The hypothesis that divalproex monotherapy is more effective than lithium monotherapy in the long-term management of rapid cycling bipolar disorder was not supported by these data. The findings raise concerns that lithium may currently be underutilized as a treatment for rapid cycling bipolar disorder and underscore the importance of combination therapy (lithium plus divalproex) in this subgroup of treatment-refractory patients.

A double-blind placebo-controlled prophylaxis trial[24] examined the efficacy of lamotrigine in patients with rapid cycling bipolar I or II disorder. Of the 60 patients stable for 6 months of treatment, 41% (37/90) were treated with lamotrigine monotherapy and 26% (23/87) were treated with placebo, which was a statistically significant difference. However, the difference between placebo and lamotrigine was not significant for bipolar I patients.

In a study by Sanger et al.[25] olanzapine and placebo were given to patients (N = 45) with a history of rapid cycling for 3 weeks. The manic symptoms of the patients were reduced from moderate-to-severe to mild levels with olanzapine therapy but not with placebo, whereas olanzapine and placebo reduced depressive symptoms at a similar rate. A long-term study[26] of olanzapine as adjunctive therapy to mood stabilizers, which included patients with rapid cycling, found statistically significant reductions in manic and depressive symptoms. Finally, in the trial[16] of olanzapine and olanzapine/fluoxetine combination in acute depression, 37% of the patients had rapid cycling, but the effect of the treatments on these patients was not explicitly discussed.

The group also proposed valproate as being beneficial for patients with rapid cycling. A prospective, open-label, long-term trial[27] found that acute and prophylactic responses with valproate were most notable for patients with mania and mixed states. In a recent maintenance study[22] comparing lithium with divalproex, approximately half of patients were stabilized with treatment.

As many of these studies show, manic symptoms are more likely to respond to treatment than depressive symptoms in bipolar patients with rapid cycling. In fact, for many patients with rapid cycling, depression tends to be the most prominent pole.[28] Thus, clinicians may find themselves faced with patients who are taking 2 or 3 of the recommended agents and still have depressive symptoms. The group agreed that when confronted with such patients, clinicians could consider augmenting with an antidepressant (e.g., an SSRI) as a last resort.

Psychosis

The group accorded that for patients who continue to have depressive symptoms and are psychotic, clinicians should consider adding olanzapine, olanzapine/fluoxetine combination, or ECT. Narendran et al.[29] reported that 3 of 4 patients with psychotic bipolar depression were much or very much improved after at least 3 months of olanzapine augmentation. Further, data from 2 double-blind placebo controlled olanzapine trials were pooled by Baldessarini and colleagues[30] to test

for differences among patient subgroups, which included patients with psychotic features. Although the trials analyzed were for the effectiveness of olanzapine in acute mania, the pooled data validated the efficacy of olanzapine over placebo for improving depressive and psychotic features associated with mania. If properly studied, other atypical antipsychotics are likely to exhibit efficacy in patients with bipolar depression with psychosis as well. In the trial[16] of olanzapine and olanzapine/fluoxetine combination in the acute treatment of bipolar I depression, 12.5% of the patients had psychotic features, although the effect of the treatments on these patients was not explicitly discussed. ECT has been found to be efficacious for patients with bipolar depression resistant to treatment.[31] Additionally, after reviewing the literature on the treatment of acute bipolar depression, Srisurapanont et al.[32] recommended ECT as a promising treatment for bipolar patients, especially for those patients who are psychotic or treatment resistent.

The group emphasized that these suggestions are not sequential and that clinicians may find it necessary to use one treatment in favor of another depending on patient symptoms and severity of symptoms. Members lamented the lack of data on effective treatment in patients with mood-congruent versus mood-incongruent psychosis.

Breakthrough Mania

For patients with bipolar depression who experience breakthrough mania, the group offered that clinicians should initially optimize whatever first-line treatment patients are taking. The members suggested that if the mania continued after optimization, several agents with varying categories of evidence are available to treat the breakthrough symptoms. Again, the group believed long-term studies in recently depressed patients were necessary for drugs to be classified as category 1.

Category 1 Evidence

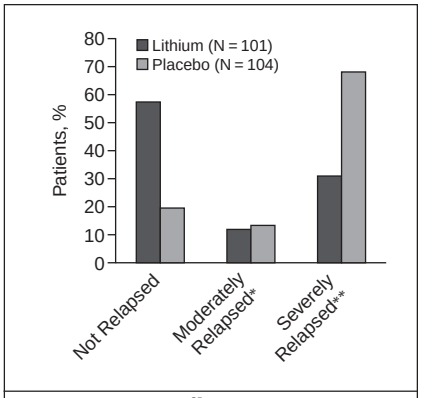
The medication with category 1 evidence for treating mania is lithium. As demonstrated earlier, this agent has been found to be an efficacious treatment for acute and long-term bipolar depression.[2,9–11] Lithium also has proven efficacy in breakthrough mania as well as the long-term treatment of mania.

Because lithium is a standard treatment for mania, in most breakthrough mania trials, lithium is the baseline medication rather than the augmenting agent. However, in a 3-week randomized placebo-controlled trial by Chou et al.,[33] lithium was added to haloperidol. Patients (N = 63) with acute bipolar mania were randomly assigned to a high (25 mg/day) or low (5 mg/day) dose of haloperidol that was augmented with placebo, standard lithium treatment, or 4 mg/day of lorazepam. Patients who received low-dose haloperidol and lithium were markedly improved compared with patients who received low-dose haloperidol and placebo. These outcomes led the study's authors to conclude that lithium augmentation enhanced antipsychotic treatment for acute mania.

A long-term trial[34] compared lithium and carbamazepine monotherapy with the combination of the 2 agents. Lithium and the combination were found to be substantially more effective at preventing mania than carbamazepine, with approximately one third of patients in the combination group experiencing no mania. For patients with rapid cycling, the combination was significantly ($p < .05$) more effective than either monotherapy.

There is reason to believe that long-term studies of lithium monotherapy also add support for its use in breakthrough mania. Prien et al.[35] conducted a 2-year randomized placebo-controlled trial of lithium prophylaxis in 205 bipolar patients who had been recently hospitalized for mania. Of the patients treated with lithium (N = 101, median dose = 1000 mg/day), 57% did not relapse during the treatment period compared with only 19% of the placebo patients (Figure 4). Severe relapses were reported in 67% of the placebo group and 31% of the lithium group, which was a significant difference ($p < .001$). Manic relapses were the most common type of relapse in both treatment groups. The outcomes of this study led the authors to conclude that lithium was effective and safe for preventing relapse in bipolar patients.

Figure 4. Treatment Outcome for Recently Manic Bipolar I Patients After Prophylactic Treatment With Lithium or Placebo[a]



[a]Data from Prien et al.[35]
*Patients with at least 1 moderate relapse but no severe relapse.
**Patients with at least 1 severe relapse.

More recent research by Bowden and colleagues[15] confirmed these earlier lithium findings. In a placebo-controlled long-term trial comparing lithium with lamotrigine in recently manic or hypomanic patients, lithium prevented the relapse or recurrence of manic, hypomanic, or mixed episodes statistically significantly better than placebo.

Category 2 Evidence

The group allowed that several atypical antipsychotics (Table 4) and valproate should be considered as category 2 evidence add-on agents in breakthrough mania since each has proven efficacy in mania.

Olanzapine. The efficacy of olanzapine in breakthrough mania was researched by Tohen et al.[36] in a 6-week double-blind randomized placebo-

Table 4. Acute Evidence for the Use of Atypical Antipsychotics as Augmenting Agents in Bipolar Depressed Patients With Breakthrough Mania

Study	N	Treatments	Length (wk)	Efficacy in Mania
Tohen et al[36]	344	OLA + (Li or VAL) vs PBO + (Li or VAL)	6	OLA + (Li or VAL) > PBO + (Li or VAL)
Sachs et al[40]	156	RIS + (Li or DIV) vs HAL + (Li or DIV) vs PBO + (Li or DIV)	3	RIS + (Li or DIV) = HAL + (Li or DIV) > PBO + (Li or DIV)
Yatham et al[41]	151	RIS + (Li or DIV or CAR) vs PBO + (Li or DIV or CAR)	3	RIS + (Li or DIV or CBZ) > PBO + (Li or DIV or CBZ)
DelBello et al[44]	30	QUE + DIV vs PBO + DIV	6	QUE + DIV > PBO + DIV
Mullen et al[45]	191	QUE + (Li or DIV) vs PBO + (Li or DIV)	3	QUE + (Li or DIV) > PBO + (Li or DIV)
Mullen and Paulsson[46]	402	QUE + (Li or DIV) PBO + (Li or DIV)	3	QUE + (Li or DIV) > PBO + (Li or DIV)
Keck et al[48]	262	ARI vs PBO	3	ARI > PBO
Bourin et al[49]	347	ARI vs HAL	12	ARI > HAL
Keck et al[51]	210	ZIP vs PBO	3	ZIP > PBO

Abbreviations: ARI = aripiprazole, CAR = carbamazepine, DIV = divalproex, HAL = haloperidol, Li = lithium, QUE = quetiapine, OLA = olanzapine, PBO = placebo, RIS = risperidone, VAL = valproate, ZIP = ziprasidone. Symbol: > = more effective than.

controlled trial. Olanzapine or placebo was added to ongoing treatment with lithium or valproate in patients (N = 344) in a manic or mixed episode who had not fully responded to at least 2 weeks of lithium or valproate prior to the start of the study. The Young Mania Rating Scale (YMRS) scores of patients in the olanzapine group (N = 229) decreased statistically significantly more than the scores of the placebo group (N = 115). Response rates were higher in the olanzapine group as well. In addition to improving mania, augmenting with olanzapine improved depression symptoms significantly more than mood stabilizer monotherapy ($p < .001$).

Similarly, in a randomized double-blind placebo-controlled 12-month trial,[37] olanzapine monotherapy was found to significantly ($p < .001$) prolong time to relapse to a manic, depressive, or mixed episode. About 47% of patients treated with olanzapine (N = 225, 5 to 20 mg/day) relapsed compared with approximately 80% of placebo-treated patients (N = 136). Depressive episodes were more common (35%) than manic episodes (16%) in olanzapine-treated patients.

Valproate. Müller-Oerlinghausen and colleagues[38] researched valproate as an add-on treatment to neuroleptics in acute mania in a 3-week randomized double-blind placebo-controlled study. Patients meeting ICD-10 criteria for acute mania were randomly assigned to valproate (mean daily dose = 19.6 mg/kg, N = 69) or placebo (N = 67). Mean neuroleptic dose was the primary outcome measure. In the valproate group, neuroleptic doses declined throughout the study, but only minor changes in doses were seen in the placebo group. In addition, statistically significantly more patients taking add-on valproate responded to treatment, as assessed by the YMRS, than did patients taking add-on placebo.

Divalproex was compared with lithium and placebo in a randomized, placebo-controlled 12-month trial.[39] After an open-label phase, patients (N = 372) who had recovered from a manic episode were randomly assigned to 1 of the 3 maintenance treatments. None of the treatments differed substantially on the primary measure, time to recurrence of any mood episode, but divalproex showed a slight difference over lithium. Further, divalproex treatment proved to be more advantageous than lithium and placebo on several secondary measures, including discontinuing treatment due to the recurrence of a mood episode and controlling subsyndromal depressive symptoms. The authors of this study provided more analyses of their findings in a later article[7] and concluded that divalproex improved the course of depressive episodes and diminished occurrence of depressive relapse in bipolar patients. The effects of divalproex were seen especially in patients who responded during manic episodes and who had more severe bipolar disorder.

Risperidone. In a 3-week acute mania trial,[40] risperidone was found to be effective in combination with mood stabilizers. Bipolar patients (N = 156) currently experiencing a manic or mixed episode were randomly assigned to risperidone (mean modal dose = 3.8 mg/day), haloperidol (mean modal dose = 6.2 mg/day), or placebo in addition to lithium or divalproex. At endpoint, patients treated with risperidone and haloperidol had statistically significantly lower YMRS scores than did placebo-treated patients. For patients who had been taking a mood stabilizer prior to entering the trial but who nonetheless experienced a manic or mixed episode, i.e., a breakthrough episode, risperidone and haloperidol augmentation decreased their YMRS scores by approximately 15 points, which was twice as much as placebo. A study by Yatham et al.[41] that compared the addition of risperidone or placebo to ongoing mood stabilizer treatment had similar results. In this 3-week trial, bipolar patients with a manic or mixed episode who had been taking lithium, divalproex, or carbamazepine for at least 2 weeks were randomly assigned to add-on risperidone (mean modal dose = 4 mg/day, N = 75) or placebo (N = 76). At week 1, the YMRS scores of risper-

idone-treated patients had substantially declined compared with the scores of placebo-treated patients, and by endpoint, scores in the risperidone group had dropped by about 14 points while the scores in the placebo group dropped about 10 points.

Data concerning the long-term efficacy of risperidone in bipolar patients with breakthrough episodes are promising. Patients (N = 12) were given adjunctive risperidone (mean = 2.75 mg/day) for a mean of 6 months.[42] One third of patients discontinued treatment due to lack of efficacy or adverse events, but half of the remaining patients showed substantial improvement. No patient reported a manic episode, although 1 depressive episode was reported. In a larger, open trial, Vieta et al.[43] added risperidone to ongoing mood stabilizer treatment in patients (N = 541) diagnosed with DSM-IV schizoaffective disorder or bipolar disorder who were currently experiencing a mood episode. Throughout the study, patients showed significant ($p < .0001$) improvement on outcome measures such as the YMRS and HAM-D.

Quetiapine. Quetiapine was investigated as an adjunctive treatment for acute mania in a 6-week double-blind, randomized, placebo-controlled study in adolescents with bipolar disorder (N = 30).[44] Patients aged 12 to 18 years experiencing a manic or mixed episode were given divalproex, 20 mg/kg, and randomly assigned to receive quetiapine, titrated to 450 mg/day, or placebo. The decrease in YMRS scores from baseline to endpoint was significantly greater in the quetiapine group compared with the placebo group ($p = .03$). Response rates were also significantly higher in the quetiapine-treated patients than in placebo-treated patients. More recent double-blind placebo-controlled adult studies[45,46] in which quetiapine was added to lithium or divalproex for acute mania have findings similar to those of this adolescent study.[44]

In an open long-term follow-up study by Ghaemi and colleagues,[47] 41 bipolar I patients with rapid cycling received quetiapine either with or without a mood stabilizer for up to 1 year. Patients were assessed using the HAM-D and YMRS, among other scales. Depression and manic symptoms improved with quetiapine treatment beginning at week 2, and the authors of this study concluded that quetiapine was an effective long-term treatment for patients with rapid cycling bipolar disorder.

Aripiprazole. Keck et al.[48] researched the efficacy of aripiprazole in acute bipolar mania in a placebo-controlled double-blind study. Patients (N = 262) experiencing an acute manic or mixed episode were randomly assigned to aripiprazole, 30 mg/day (dose could be halved for tolerability), or placebo for 3 weeks. Mean change in YMRS score and response (defined as $\geq 50\%$ reduction in YMRS score from baseline) were used as outcome measures. The YMRS scores of aripiprazole-treated patients dropped a mean of 8.2 points while the scores of placebo-treated patients dropped a mean of 3.2 points. This difference was statistically significant. Almost twice as many patients taking aripiprazole as patients taking placebo responded to treatment (40% versus 19%), which was also a significant difference ($p \leq .005$).

Aripiprazole was compared with haloperidol in a 12-week study of acute mania.[49] Patients with bipolar disorder (N = 347) were randomly assigned to aripiprazole, 15 mg/day, or haloperidol, 10 mg/day. By study end, statistically significantly more aripiprazole-treated patients had responded to and continued with treatment than haloperidol-treated patients.

Patients recently completing an acute mania study of aripiprazole or recently experiencing a manic episode entered a 26-week double-blind placebo-controlled trial of aripiprazole.[50] Time to relapse (i.e., hospitalization, change in medication, discontinuation due to lack of efficacy) for manic, mixed, or depressive symptoms was the primary endpoint. Throughout the study, fewer patients treated with aripiprazole relapsed than did patients treated with placebo. Of those aripiprazole-patients who did relapse, depressive relapse was most common, followed by manic relapse and then mixed relapse.

Ziprasidone. In a 3-week study,[51] bipolar patients (N = 210) currently experiencing a manic or mixed episode were randomly assigned to ziprasidone, 40 to 80 mg/b.i.d, or placebo. Ziprasidone-treated patients showed substantial improvement as early as 2 days into the study and maintained that improvement until study end.

Category 3 Evidence

Clozapine and some of the typical antipsychotic agents meet criteria for category 3 evidence and were therefore offered by the group as augmenting agents in breakthrough mania. In a trial by Suppes et al.,[52] patients with treatment-resistant schizoaffective or bipolar disorder were randomly assigned to adjunctive clozapine (N = 19) or treatment as usual, i.e., no clozapine (N = 19). Patients taking clozapine showed more clinical improvement than those not taking clozapine, and clozapine proved to have substantial antimanic and mood-stabilizing properties. The group acknowledged that typical antipsychotics have not been extensively studied in breakthrough mania but are extensively used depending upon the culture.

Response

The group agreed that, since bipolar disorder is a lifelong illness, patients who respond to their first-line treatment should continue that treatment for the long-term. Controlled evidence is available for the efficacy and safety of lithium for 2 years,[2] lamotrigine for 18 months,[14] olanzapine in recently manic patients for 1 year,[37] and olanzapine and olanzapine/fluoxetine combination in recently depressed patients for 8 weeks.[16]

Effective Clinical Management

The group concurred that clinicians should consider the individual patient when deciding what first-line agent to use in bipolar depression as well as deciding what treatment to use for patients whose response to treatment is inadequate. For example, for bipolar patients with a history of serious mania, lithium may be preferred because of its efficacy for delaying manic episodes; whereas, for bipolar patients with a history of serious depression, lamotrigine may be preferred because of its efficacy for delaying depressive episodes.[14] For patients who are nonresponsive to treatment with severe psychosis, the most effective option may be ECT rather than another pharmacologic treatment.

The group also emphasized that although they focused their guidelines mainly on drug therapy, all patients with bipolar disorder should be treated with psychological treatments in additional to any pharmacologic treatment. Psychosocial treatments such as cognitive therapy (CT) and psychoeducation have been shown to prevent bipolar relapse and improve social functioning and treatment compliance. In a 12-month randomized controlled study, Lam et al.[53] compared the effectiveness of CT designed to prevent episode relapse with no CT treatment in 103 patients diagnosed with DSM-IV bipolar I disorder. Throughout the study, fewer patients treated with CT than in the control group experienced episode recurrence, and for those in the CT group who did relapse, episodes were shorter than for controls. Additionally, CT ameliorated mood symptoms and improved social functioning in these patients.

Psychoeducation increases compliance in bipolar patients,[54] but this psychosocial treatment clearly has other benefits as well. A randomized trial[54] of group psychoeducation for relapse prevention had outcomes similar to those of the CT study. Bipolar patients (N = 60) who participated in group psychoeducation had statistically significantly fewer episode recurrences than bipolar patients in the control group (N = 60) who received no psychoeducation. Time to relapse was increased and number of hospitalizations decreased with psychoeducation. In another study,[55] the same authors researched the efficacy of psychoeducation in fully compliant patients. Again, relapse occurred statistically significantly less often in patients treated with psychoeducation compared with controls who received no psychoeducation. Further, psychoeducated patients had significantly fewer total relapses and depressive episodes. Such evidence reiterates the importance of multimodal management for bipolar treatment.

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Drug names: *aripiprazole (Abilify), bupropion (Wellbutrin and others), carbamazepine (Tegretol, Epitol, and others), clozapine (Clozaril and others), desipramine (Norpramin and others), divalproex (Depakote), haloperidol (Haldol and others), imipramine (Tofranil and others), lamotrigine (Lamictal), lithium (Eskalith, Lithobid, and others), lorazepam (Ativan and others), olanzapine (Zyprexa), olanzapine/fluoxetine combination (Symbyax), quetiapine (Seroquel), risperidone (Risperdal), venlafaxine (Effexor), ziprasidone (Geodon).*

Financial disclosure: Dr. Calabrese *has received funding from National Institute of Mental Health, Abbott, Ciba-Geigy, Merck, GlaxoSmithKline, Janssen, Eli Lilly, MacArthur Foundation, National Alliance for Research in Schizophrenia and Affective Disorders, Parke-Davis, Robert Wood Johnson, Sandoz Pharmaceuticals, Stanley Foundation, Tap Holdings, UCB Pharma, and Wyeth, and has consulting agreements with and is on advisory boards of Abbott, AstraZeneca, Bristol-Myers Squibb, Otsuka, Eli Lilly, GlaxoSmithKline, Janssen-Cilag, Novartis, Parke-Davis, Warner Lambert, Robert Wood Johnson, Shire Richwood, TAP Pharmaceuticals, Teva Pharmaceuticals, UCB Pharma.* ***Dr. Kasper*** *is a consultant for and is on the advisory boards of AstraZeneca, Bristol-Myers Squibb, GlaxoSmithKline, Eli Lilly, Lundbeck, Pfizer, Organon, Janssen, and Novartis; has received grant/research support from Eli Lilly, Lundbeck, Bristol-Myers Squibb, GlaxoSmithKline, Organon and Servier; and is on the speaker's bureaus of AstraZeneca, Eli Lilly, Lunbeck, and Janssen.* ***Dr. Johnson*** *is a consultant for Novartis and is on the speakers/advisory boards for Bristol-Myers Squibb, GlaxoSmithKline, and Sanofi-Synthelabo.* ***Dr. Tajima*** *is a consultant for Solvay and Shionogi and is on the speakers/advisory boards for GlaxoSmithKline, Janssen, Solvay, Meiji Pharmaceutical, Fujisawa Healthcare, Otsuka, and Sumitomo Pharmaceutical.* ***Dr. Vieta*** *is a consultant for AstraZeneca, Bristol-Myers Squibb, Eli Lilly, Janssen-Cilag, and Novartis; has received grant/research support from AstraZeneca, Eli Lilly, Janssen-Cilag, GlaxoSmithKline, and Sanofi-Sythelabo; and is on the speakers/advisory boards for Pfizer, GlaxoSmithKline, Bristol-Myers Squibb, AstraZeneca, Eli Lilly, Janssen-Cilag, and Lundbeck.* ***Dr. Yatham*** *is a consultant for, has received grant/research support and honoraria from, and is on the speakers/advisory boards for GlaxoSmithKline, Janssen, Eli Lilly, AstraZeneca, and Bristol-Myers Squibb.* ***Dr. Young*** *has no significant commercial relationship to disclose relative to the presentation.*

To cite a section from this ACADEMIC HIGHLIGHTS, follow the format below:
Calabrese JR, Kasper S, Johnson G, Tajima O, Vieta E, Yatham LN, Young AH. International Consensus Group on Bipolar I Depression Treatment Guidelines [ACADEMIC HIGHLIGHTS]. J Clin Psychiatry 2004;65:569–579