International Consensus Group on the Evidence-Based Pharmacologic Treatment of Bipolar I and II Depression

This ACADEMIC HIGHLIGHTS section of The Journal of Clinical Psychiatry *presents the highlights of the International Consensus Group (ICG) meeting held in October 2007 to reevaluate clinical trial data on the treatment of bipolar I depression published since the initial guidelines were presented in April 2004.[1] This report was supported by an educational grant from AstraZeneca following a request from the ICG members to update the existing publication.*

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Overview

In 2004, an International Consensus Group (ICG) developed and published recommendations for the treatment of bipolar I depression based on available clinical evidence.[1] The ICG reconvened in October 2007 to reevaluate clinical trial data published in the intervening years on the treatment of bipolar I depression. In addition, the ICG extended the scope of its discussions to consider published evidence for the treatment of bipolar II depression and also special populations of patients with bipolar depression.

As in 2004, the ICG agreed that these recommendations should be based on the available clinical evidence rather than expert opinion, in order to encompass all pharmacologic agents that have been evaluated for the treatment of bipolar depression.

Introduction

Bipolar disorder is a severe, long-term illness with a lifetime prevalence of approximately 2% that is characterized by cyclical episodes of mania and depression[2,3] and has been the topic of a number of comprehensive publications.[4] The impact of bipolar disorder on the patient is highly significant, such that bipolar disorder leads to 2% of all disability-adjusted life-years associated with noncommunicable disease worldwide.[5] The degree of disability associated with episodes of bipolar depression is disproportionately greater compared with episodes of bipolar mania,[6] and patients with bipolar depression experience significantly greater psychosocial impairment.[7] This is of particular importance given that patients with bipolar I disorder are likely to experience depressive symptoms approximately 3 times more frequently than symptoms of mania.[8,9] Furthermore, beyond the high frequency of episodes, bipolar depression is a major cause of suicide, such that the lifetime prevalence of a suicide attempt is approximately 29% in these patients.[10]

The considerable impact and frequency of episodes of bipolar depression emphasize the importance of effectively managing depressive symptoms to achieve the ultimate goal of mood stabilization. However, a key challenge in bipolar disorder is the accurate diagnosis of the illness. Several factors that confound the diagnosis and treatment of bipolar disorder include a considerable symptomatic overlap with other psychiatric illnesses, an incomplete medical history of the patient, and lack of patient insight. Treatment is complicated further by the high prevalence of comorbidities such as anxiety disorders and substance use disorders in these patients. These comorbidities can have a detrimental effect on the disease course, including an increase in the number of suicide attempts.[11–14] A combination of these factors can lead to bipolar disorder being underdiagnosed or misdiagnosed as major depressive disorder, anxiety disorder, or schizophrenia, with reported rates of misdiagnosis as high as 69%.[15] Inaccurate diagnosis can result in the implementation of inappropriate treatment, which can ultimately compromise long-term outcomes. Potential steps that could be taken in order to improve diagnosis of bipolar disorder

include investigating the presence of manic/hypomanic, psychotic, or reverse vegetative symptoms in every patient presenting with depressive symptoms and also establishing whether the patient has a family history of bipolar disorder.

An additional issue regarding the diagnosis of bipolar depression is that there is some degree of controversy regarding the lack of accepted diagnostic criteria. To address this, a "probabilistic" approach to the diagnosis of bipolar I depression has recently been proposed.[16] This approach focuses on the most commonly reported symptoms in patients with bipolar depression, such as hypersomnia, increased weight, and manic symptoms, compared with those symptoms most commonly reported in patients with major depression, such as reduced sleep and weight loss. These recommendations propose that the combination of 4 or 5 or more of these defined symptoms should increase the likelihood of diagnosis of either bipolar or major depression.

An authoritative treatise was recently published that reviewed the scientific literature regarding the diagnostic and therapeutic approaches to manic-depressive illness, including both bipolar disorders and recurrent depressive disorders.[17] Here, we describe the recent evidence for therapeutic options in bipolar I and bipolar II depression. This update to the ICG 2004 recommendations has been developed based on a comprehensive literature review in order to provide an evidence base of published treatments in bipolar depression.

Developing Treatment Recommendations: Categories of Evidence

As in 2004, the group prioritized their recommendations on the basis of clinical evidence. The categories proposed in the 2004 ICG publication were based on the limited data available at that time, and, given the increased volume of studies describing a wider range of pharmacologic treatments in the intervening period, the original categories were considered insufficient to provide meaningful clinical recommendations. Therefore, the ICG revisited and redefined the criteria used to assign categories of evidence (Table 1).

Table 1. Definitions of the Categories of Evidence Used to Classify Pharmacologic Treatments for Bipolar Depression

Category 1 Evidence of efficacy in randomized, placebo-controlled trial(s) in treatment of acute bipolar depression and long-term[a] treatment for both poles of illness in both recently[b] depressed and recently[b] manic patients
Category 2 Evidence of efficacy in randomized, controlled trial(s) in acute and long-term[a] treatment of bipolar depression without treatment-emergent mania/mixed states/cycle acceleration
Category 3 Evidence of efficacy in randomized, controlled trial(s) in acute treatment of bipolar depression without treatment-emergent mania/mixed states
[a]Long-term = 6 months or longer. [b]Recent = index episode within last 3 months.

Agents satisfying category 1 evidence were required to have data from at least 1 randomized, placebo-controlled trial in both the short- and long-term treatment of bipolar I or bipolar II depression. Furthermore, long-term evidence was needed from at least 1 trial of this design documenting the efficacy of the agent in patients experiencing both recent episodes of depression and recent episodes of mania.

An agent meeting category 2 evidence was required to have data from at least 1 randomized, controlled trial in both the short- and long-term treatment of bipolar depression, but there should be no evidence of treatment-emergent mania, mixed states, or cycle acceleration. Furthermore, the ICG members did not require index episodes of depression in order for a study to be considered category 2 evidence.

The final category of evidence (category 3) was assigned to agents with data from at least 1 randomized, controlled trial in the acute treatment of bipolar depression without treatment-emergent mania and mixed states.

For each agent, a summary of available clinical evidence supporting use in the acute setting is presented first, followed by a summary of clinical evidence from trials investigating the long-term use (defined as 6 months or longer) of the treatment, where applicable.

Treatments for the Management of Bipolar I Depression

Category 1 Evidence

Three agents, lithium, lamotrigine, and quetiapine (all as monotherapy), met category 1 evidence for both the acute and long-term treatment of bipolar I depression (Table 2).

Lithium (monotherapy). Recent clinical evidence in bipolar I depression consolidated the classification of lithium monotherapy as a category 1 agent. Evidence supporting the use of lithium monotherapy for the acute treatment of bipolar I depression has been described in a review of short-term, placebo-controlled, double-blind, crossover trials that compared the efficacy of lithium with placebo.[18] Of the 8 studies included in the review, 7 reported that lithium was significantly more effective than placebo. Across these studies, a mean response rate of 76% (range, 64%–100%) with lithium was reported. Furthermore, 52% (range, 38%–70%) of patients experienced a relapse of depressive symptoms when lithium was substituted for placebo.[18]

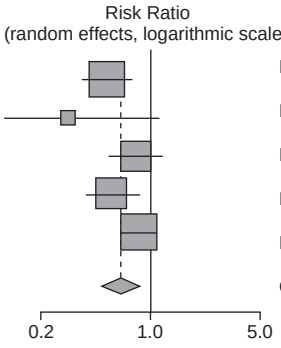
In contrast to the older literature reviewed above, a more recent

Table 2. Summary of the Classification of Pharmacologic Treatments for Bipolar I Depression Based on the Level of Available Clinical Evidence[a]

Category	Agents With Positive Evidence	Agents With Negative Evidence
Category 1	Lithium (monotherapy) Lamotrigine (monotherapy) Quetiapine (monotherapy)	None
Category 2	Olanzapine (monotherapy) Olanzapine/fluoxetine combination Lamotrigine (adjunctive) Quetiapine (adjunctive)	Imipramine (adjunctive)
Category 3	Divalproex (monotherapy) Carbamazepine (monotherapy) Fluoxetine (monotherapy) Sertraline (adjunctive) Bupropion (adjunctive) Modafinil (adjunctive) Pramipexole (adjunctive) Ethyl-eicosapentaenoic acid (adjunctive)	Paroxetine (monotherapy and adjunctive) Aripiprazole (monotherapy)

[a]Treatments for bipolar II depression are not included due to the lack of category 1 agents and small number of category 2 and 3 agents.

Figure 1. Results From a Meta-Analysis of Randomized, Placebo-Controlled Trials to Evaluate the Effectiveness of Lithium in the Prevention of Any Relapse (depression or mania) in Patients With Bipolar Disorder[a]



Trial	Risk Ratio (95% CI)	Relapse Rate: Lithium	Relapse Rate: Placebo
Prien et al 1973	0.53 (0.41 to 0.67)	43% (43/101)	81% (84/104)
Kane et al 1982[c]	0.3 (0.08 to 1.10)	20% (2/10)	67% (8/12)
Bowden et al 2000	0.80 (0.54 to 1.20)	31% (28/91)	38% (36/94)
Bowden et al 2003	0.56 (0.38 to 0.83)	39% (18/46)	70% (49/70)
Bowden et al 2002	0.85 (0.66 to 1.09)	46% (56/121)	54% (66/121)
Overall (95% CI)	0.65 (0.50 to 0.84)	40% (147/369)	60% (243/401)

[a]Reprinted with permission from Geddes et al.[22]
[b]The area of the gray box represents the weighting given to the trial in the overall pooled estimate and takes into account the number of participants and events and the amount of between-studies variation (heterogeneity).
[c]Lower confidence interval extends beyond graph (0.08).

double-blind, randomized, placebo-controlled study of quetiapine (300 and 600 mg/day) and lithium (600–1800 mg/day) as acute monotherapy found no statistically significant difference between lithium and placebo.[19] Mean change from baseline to week 8 in Montgomery-Asberg Depression Rating Scale (MADRS) score was –13.60 for lithium and –11.81 for placebo (p = .123). Furthermore, response and remission rates did not significantly improve with lithium (62.5% and 62.5%, respectively) compared with placebo (55.8% and 55.0%, respectively). However, the mean serum lithium levels in this study were noted to be 0.61 mEq/L, and it is unknown if response rates and improvement were greater in those with higher serum lithium levels.

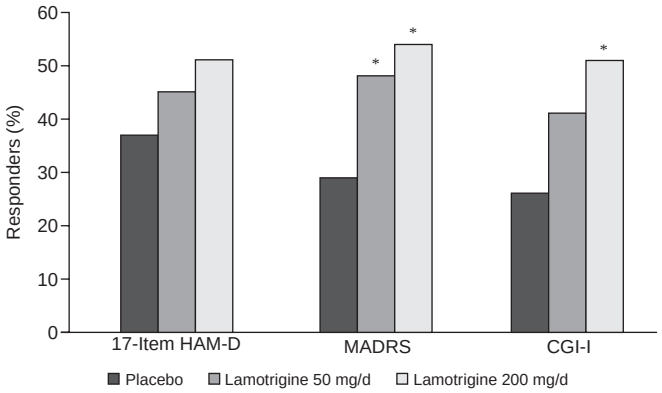
Two early studies document the efficacy of lithium in the long-term treatment of bipolar disorder. In one study, patients with bipolar disorder (N = 205), most recent episode manic, were randomly assigned to lithium or placebo for a period of 2 years.[20] The number of manic episodes, but not depressive episodes, was significantly lower with lithium compared with placebo (32 and 71, respectively; p < .001). In the other study, patients with bipolar disorder (N = 44), most recent episode depressed, were randomly assigned to lithium, imipramine, or placebo for 2 years.[20,21] In this study, the number of depressive episodes, but not manic episodes, experienced was significantly lower in the lithium group compared with the placebo group (4 and 8, respectively; p < .05).

A meta-analysis of 5 randomized, placebo-controlled trials comparing the long-term use of lithium with placebo in patients (N = 770) with bipolar disorder adds further support to the use of lithium in this setting. The authors concluded that lithium was more effective than placebo in preventing any new mood episodes (random effects relative risk = 0.65, 95% confidence interval [CI] = 0.50 to 0.84, p = .001) (Figure 1).[22] The mean risk of relapse was 60% for placebo compared with 40% for lithium. Lithium was superior to placebo in preventing manic episodes (random effects relative risk = 0.62, 95% CI = 0.40 to 0.95, p = .03), but not depressive episodes (random effects relative risk = 0.72, 95% CI = 0.49 to 1.07, p = .10).[22]

These findings are supported by a more recent systematic review of randomized, controlled trials of mood stabilizers and antipsychotics in the maintenance phase of bipolar disorder.[23] The authors reviewed 14 studies in total, of which 4 evaluated the efficacy of lithium compared with placebo in this setting. Lithium was found to be significantly more effective than placebo at preventing relapse due to any mood episode (hazard ratio [HR] 0.68, 95% CI = 0.53 to 0.86) and due to a manic episode (HR 0.53, 95% CI = 0.35 to 0.79).[23]

Additional evidence for the effectiveness of lithium as a long-term treatment for patients with bipolar disorder is provided by two 18-month, placebo-controlled trials of lamotrigine or lithium as maintenance treatment,[24,25] the former in recently manic patients and the latter in recently depressed patients,

Figure 2. Patients With Bipolar I Depression Showing a Response (HAM-D, MADRS, and CGI-I) to Treatment With Lamotrigine Monotherapy (50 mg/day or 200 mg/day) at Week 7[a,b]



[a]Adapted with permission from Calabrese et al.[27]
[b]Response defined as ≥ 50% reduction on the 17-item HAM-D or MADRS or a rating of very much improved or much improved on the CGI-I.
*p < .05 vs. placebo.
Abbreviations: CGI-I = Clinical Global Impressions-Improvement scale, HAM-D = Hamilton Rating Scale for Depression, MADRS = Montgomery-Asberg Depression Rating Scale.

both of which report similar findings. In the former, following an 8- to 16-week open phase during which patients with bipolar I disorder received lamotrigine, patients (N = 175) were randomly assigned to double-blind treatment with lithium or lamotrigine for up to 18 months. The primary endpoint was time to intervention for any mood episode, and results showed that lithium was significantly superior to placebo (p = .003).[24] These results are supported by the findings from a second 18-month, double-blind, placebo-controlled study of maintenance treatment with lithium or lamotrigine in patients with bipolar I disorder experiencing a recent depressive episode. Although lithium significantly prolonged the time to any mood episode compared with placebo (170 vs. 93 days; p = .029), lithium was statistically superior to placebo in delaying time to intervention for manic or hypomanic episodes (p = .026) but not depressive episodes (p = .209).[25]

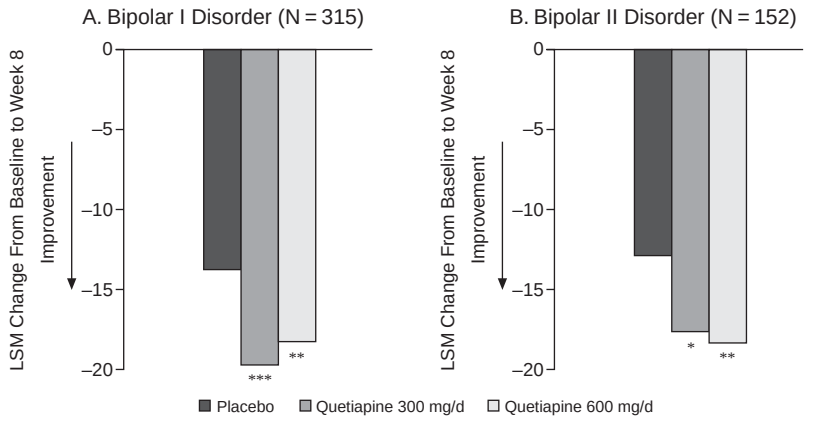
Furthermore, the possibility that the effectiveness of lithium has diminished over the course of long-term treatment has been studied.[26] A pooled analysis of data from 24 studies investigated the clinical effects of long-term lithium in 360 patients with bipolar disorder who received lithium maintenance treatment since 1970. In the period 1970–1981, the number of recurrences of mania or depression per month was 2.7%, compared with 0.5% per month in the period 1982–1996 (p = .04), suggesting that loss of effectiveness has not occurred with lithium as maintenance treatment over time.

Lamotrigine (monotherapy). Lamotrigine monotherapy continues to meet category 1 evidence for bipolar I depression, as per the previous ICG recommendations,[1] in which evidence to support this classification was derived from a double-blind, placebo-controlled study of lamotrigine monotherapy for the acute treatment of bipolar I depression.[27] In this study, outpatients with bipolar I disorder (N = 195) experiencing a major depressive episode were randomly assigned to 7 weeks' treatment with lamotrigine (50 or 200 mg/day) or placebo. Mean change from baseline analyses on the primary outcome measure, the 17-item Hamilton Rating Scale for Depression (HAM-D) total score from baseline to week 7 compared with placebo, were –9.3 for lamotrigine 50 mg/day, –10.5 for lamotrigine 200 mg/day, and –7.8 for placebo (p = NS for both doses of lamotrigine vs. placebo).[27] However, the 200 mg/day arm of lamotrigine treatment was associated with significant improvement over placebo for the secondary outcome measures, including MADRS response rates (48%, lamotrigine 50 mg/day; 54%, lamotrigine 200 mg/day; 29%, placebo; p < .05 for both doses vs. placebo) and Clinical Global Impressions-Improvement scale (CGI-I) (51%, 200 mg/day; 26%, placebo; p < .05) compared with placebo (Figure 2).[27] More recently, this study was subsequently included in a review of 5 double-blind, placebo-controlled trials, all of which investigated the use of lamotrigine in the acute treatment of bipolar depression.[28] In each of the 5 studies, no significant difference between lamotrigine and placebo was observed on primary efficacy endpoints (HAM-D in 2 studies and MADRS in 3 studies).[28] As described above, lamotrigine significantly improved secondary endpoints in 1 of the 5 studies.[27]

Additional evidence was provided by a recent meta-analysis of 5 randomized, placebo-controlled trials that investigated the efficacy of lamotrigine monotherapy for the acute treatment of bipolar depression.[29,30] Significantly higher HAM-D and MADRS response rates (≥ 50% reduction in baseline score) were reported with lamotrigine compared with placebo (HAM-D: pooled relative risk = 1.27, 95% CI = 1.09 to 1.47; p < .01; MADRS: pooled relative risk = 1.22, 95% CI = 1.06 to 1.41; p < .01). Furthermore, remission rates were significantly greater with lamotrigine than placebo on MADRS (total score < 12; pooled relative risk = 1.21, 95% CI = 1.03 to 1.42; p < .05) but not on HAM-D (total score < 8; pooled relative risk = 1.10, 95% CI = 0.90 to 1.36; p = .351).[29,30]

Support for the effectiveness of lamotrigine in bipolar I depression can also be derived from a 7-week,

Figure 3. Change in MADRS Total Score From Baseline for Patients With (A) Bipolar I or (B) Bipolar II Depression Treated With Placebo or Quetiapine Monotherapy (300 or 600 mg/day) at Week 8[a]



[a]Data from Thase et al.[34]
*p < .05, **p < .01, ***p < .001 vs. placebo.
Abbreviations: LSM = least squares mean, MADRS = Montgomery-Asberg Depression Rating Scale.

randomized, double-blind trial (N = 410).[31] In this study, olanzapine/fluoxetine combination (OFC) was significantly better in improving depressive symptoms compared with lamotrigine, as measured by change in Clinical Global Impressions-Severity of Illness scale (CGI-S) (p < .01) and MADRS (p < .01) total scores, but lamotrigine demonstrated a more favorable safety profile compared with OFC.

Two long-term studies[24,25] that compared the effectiveness of lithium and lamotrigine monotherapy over a period of 18 months in patients with bipolar I disorder and recent episodes of mania or depression were discussed in the ICG 2004 recommendations.[1] The primary endpoint in both studies was time to intervention for any mood episode. Bowden et al.[24] demonstrated that lamotrigine was significantly more effective than placebo at prolonging the time to intervention for any mood episode (p = .02) and specifically time to a depressive episode (p = .02). This finding is supported by the study by Calabrese et al.[25] that again found that lamotrigine significantly prolonged time to any mood episode (p = .029) and a depressive episode (p = .047). A pooled analysis of data from these trials showed that lamotrigine, but not lithium, was superior (p = .009) to placebo at delaying the time to intervention for a depressive episode.[32]

Quetiapine (monotherapy). The ICG agreed that, based on clinical evidence available since 2004, quetiapine monotherapy should be classified as a category 1 treatment for bipolar I depression. Evidence for the acute efficacy of quetiapine monotherapy in patients with bipolar I or bipolar II depression is provided by the results of 2 large, 8-week, randomized, double-blind, placebo-controlled studies that evaluated quetiapine monotherapy (300 and 600 mg/day).[33,34]

The primary efficacy variable in both studies was mean change in MADRS total score from baseline to week 8. In the first study, quetiapine monotherapy at both doses significantly improved MADRS total scores in patients with bipolar I depression (N = 360) compared with placebo at week 8 (–18.05, quetiapine 600 mg/day; –16.91, quetiapine 300 mg/day; –9.24, placebo; p < .001 for both quetiapine doses vs. placebo). Moreover, this effect was seen as early as week 1. These findings were confirmed in the second study, which was an identically designed study. Mean change in MADRS total score from baseline to week 8 in patients with bipolar I depression (N = 338) was –13.73 for placebo, –18.23 for quetiapine 600 mg/day (p < .01 vs. placebo), and –19.65 for quetiapine 300 mg/day (p < .001 vs. placebo) (Figure 3A).[34]

In the first study,[33] effect sizes (based on change in MADRS total score from baseline to week 8) in patients with bipolar I depression were 0.91 and 1.09 for quetiapine 300 and 600 mg/day, respectively. In the second study,[34] effect sizes at week 8 for the bipolar I subgroup were 0.67 and 0.51 for quetiapine 300 and 600 mg/day, respectively. Furthermore, treatment-emergent mania rates (defined as the proportion of patients with a Young Mania Rating Scale [YMRS] total score ≥ 16 on any 2 consecutive visits or at final assessment) for the quetiapine 300 mg/day, quetiapine 600 mg/day, and placebo groups were 3.9%, 2.2%, and 3.9%, respectively, in the Calabrese et al. study[33] and 1.8%, 3.6%, and 6.6%, respectively, in the Thase et al. study.[34]

The efficacy of quetiapine or lithium as acute monotherapy was further evaluated in a double-blind, placebo-controlled study in patients with bipolar I and bipolar II depression.[19] The study consisted of an initial acute phase lasting 8 weeks during which patients were randomly assigned to receive quetiapine 300 mg/day, quetiapine 600 mg/day, lithium, or placebo. This was followed by a continuation phase lasting between 26 and 52 weeks. The primary endpoint of the acute phase of the study was the change from baseline to week 8 in MADRS total score. In the bipolar I subgroup of patients (N = 487), the mean change in MADRS total score at week 8 was –14.8 with quetiapine 300 mg/day (p < .05 vs. placebo) and –16.5 with quetiapine 600 mg/day (p < .05 vs. placebo) compared with –11.2 for placebo.[19]

These findings are consistent with a double-blind, placebo-controlled

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study[35] of similar design that evaluated the efficacy of quetiapine (300 mg/day and 600 mg/day) and paroxetine (20 mg/day) as monotherapy in patients with bipolar I and bipolar II depression. In the bipolar I subgroup (N = 448), quetiapine 600 mg/day significantly reduced MADRS total score from baseline to week 8 (–16.2, quetiapine 300 mg/day [$p < .05$] and –16.4, quetiapine 600 mg/day [$p < .05$] compared with placebo [–13.4]). Both of the above studies were sufficiently large to provide adequate evidence for the short- and long-term use of quetiapine monotherapy for the treatment of bipolar I or II depression.[19,35] These 2 studies were powered to allow for a combined continuation phase, during which patients who remitted on treatment with quetiapine 300 mg/day or 600 mg/day were randomly reassigned to either continued treatment on quetiapine 300 mg/day or placebo and were studied for an additional 26 to 52 weeks. Quetiapine significantly increased the time to recurrence of depression compared with placebo (HR = 0.48, 95% CI = 0.29 to 0.77[19] and HR = 0.36, 95% CI = 0.21 to 0.63[35]) in patients with bipolar I or II depression.

Category 2 Evidence

Olanzapine and olanzapine/fluoxetine combination. The publication of a study describing the efficacy of OFC compared with lamotrigine in patients with bipolar I depression provides additional support for olanzapine monotherapy and OFC meeting category 2 evidence. The efficacy of OFC (6/25, 6/50, 12/25, or 12/50 mg/day; N = 205) in comparison with lamotrigine (up to 200 mg/day) was demonstrated in a 7-week, randomized, double-blind, parallel-group study in patients with bipolar I depression. The primary outcome measure was change in overall bipolar status as measured by change in CGI-S score from baseline to week 7. OFC was associated with significantly greater improvement in mean CGI-S score from baseline to week 7 compared with lamotrigine (–1.43, OFC; –1.18, lamotrigine; $p < .01$). Significant differences were also observed at weeks 1, 2, 4, 5, and 6 (all $p < .05$ vs. lamotrigine). Furthermore, patients had statistically significantly greater improvement in mean MADRS total score with OFC than lamotrigine at week 7 (–14.91, OFC; –12.92, lamotrigine; $p < .01$).[31]

Further evidence supporting the category 2 status of both olanzapine and OFC was provided by a subanalysis of data from an 8-week, placebo-controlled, randomized study that investigated the efficacy of the 2 treatments in patients with bipolar I depression.[36] The aim of the analysis was to compare rates of treatment-emergent mania (defined a priori as a YMRS score < 15 at baseline and ≥ 15 at any subsequent visit) in patients receiving olanzapine (5–20 mg/day, N = 370), OFC (6/25, 6/50, or 12/50 mg/day, N = 86), or placebo (N = 377). During the 8-week study, olanzapine and OFC were not associated with a greater risk of treatment-emergent mania compared with placebo (5.7%, 6.4%, and 6.7%, respectively; $p = .861$).[37]

To date, the long-term use of olanzapine or OFC in patients with bipolar depression has not been evaluated in placebo-controlled trials. The only long-term, controlled data for olanzapine plus fluoxetine in bipolar depression derive from a study evaluating the efficacy of OFC. A 25-week, randomized, double-blind study compared the efficacy of OFC (6/25, 6/50, 12/25, or 12/50 mg/day; N = 205) and lamotrigine (maximum dose 200 mg/day, N = 205) in patients with bipolar I depression.[38] OFC was associated with significantly greater improvements in CGI-S and MADRS total scores than lamotrigine from baseline to week 25 ($p < .01$).

Adjunctive lamotrigine. The use of adjunctive lamotrigine as a treatment for bipolar I depression was investigated as part of the Systematic Treatment Enhancement Program for Bipolar Disorder (STEP-BD) study. This study was designed to evaluate the rate of recovery (defined as no more than 2 symptoms meeting *Diagnostic and Statistical Manual of Mental Disorders*, Fourth Edition [DSM-IV] threshold criteria for a mood episode and no significant symptoms present for 8 weeks) with open-label lamotrigine, inositol, or risperidone as adjuncts to a mood stabilizer for up to 16 weeks in patients (N = 66) with treatment-resistant bipolar I or bipolar II depression. Recovery rates were 23.8% (95% CI = 5.8 to 41.8) with lamotrigine compared with 17.4% (95% CI = 2.4 to 32.4) with inositol and 4.6% (95% CI = 0 to 14.6) for risperidone (no significant between-group differences were reported).[39]

In addition, the use of adjunctive lamotrigine was evaluated in an 8-week, double-blind, randomized, placebo-controlled trial.[40] Results suggested that lamotrigine in combination with lithium was superior to lithium monotherapy. Change from baseline in MADRS total score was significantly greater with lamotrigine compared with placebo ($p = .024$), and significantly more patients experienced a MADRS response with lamotrigine than placebo (51.6%, lamotrigine; 31.7%, placebo; $p < .05$).

A comparison of the adjunctive use of lamotrigine and lithium in the long-term treatment of bipolar disorder has been carried out in an open, randomized trial.[41] Patients were randomly assigned to receive lithium (dosed to obtain serum levels of 0.5–0.8 mmol/L, N = 78) or lamotrigine (up to 400 mg/day, N = 77) for up to 6 years, with concomitant pharmacologic therapy allowed for the first 6 months of the study period. The primary outcome measure was the cumulative probability of the patients requiring only monotherapy at month 6 and continuing on monotherapy after this assessment. No differences were noted between lamotrigine and lithium when used as adjunctive therapy with respect to the primary outcome measure (61.0% and 52.6%, respectively).[41]

Adjunctive quetiapine. To date, no randomized, controlled trials have examined the efficacy of adjunctive

quetiapine treatment for acute bipolar depression; however, evidence for long-term efficacy in patients with bipolar I depression is provided by 2 randomized, double-blind, parallel-group studies that investigated the use of quetiapine in combination with lithium or divalproex (Li/DVP).[42,43] In both studies, a 12- to 36-week open-label stabilization phase was followed by a randomized treatment phase of up to 104 weeks. The primary efficacy endpoint for both studies was the time to recurrence of any mood event (mixed, mania, or depression). In one study,[42] quetiapine in combination with Li/DVP was found to be significantly more effective than placebo and Li/DVP in preventing the recurrence of any mood event (HR = 0.32, 95% CI = 0.24 to 0.42, $p < .001$) and in particular a depression event (HR = 0.33, 95% CI = 0.23 to 0.48, $p < .001$). In the other study,[43] quetiapine in combination with Li/DVP was also significantly more effective than placebo and Li/DVP in preventing both the recurrence of any mood event (HR = 0.28, 95% CI = 0.21 to 0.37, $p < .001$) and a depression event (HR = 0.26, 95% CI = 0.17 to 0.41, $p < .001$).

Imipramine. A double-blind, randomized, placebo-controlled study investigated the use of adjunctive antidepressants in patients with bipolar I depression. Nemeroff et al.[44] investigated the efficacy of paroxetine, imipramine, or placebo in 117 outpatients stabilized on lithium therapy. Patients were randomly assigned to receive paroxetine (mean dose = 32.6 mg/day), imipramine (mean dose = 166.7 mg/day), or placebo for 10 weeks. Mean changes in HAM-D and CGI-S total score from baseline to week 10 in the paroxetine and imipramine groups were no different from those in the placebo group.

The long-term efficacy of imipramine and lithium for the prevention of affective episodes in patients with bipolar disorder was investigated in a 2-year, randomized, placebo-controlled study.[21] Imipramine had no effect on the number of depressive episodes experienced compared with placebo. Furthermore, there was no evidence of a protective effect against episodes of mania with imipramine, with 83%, 67%, and 12% of patients experiencing a manic episode during the last 20 months of the study with placebo, imipramine, and lithium, respectively.

Category 3 Evidence

A number of additional pharmacologic treatment options that were not included in the 2004 ICG recommendations[1] have been evaluated in the interim period for the treatment of bipolar I depression and are considered by the ICG to meet category 3 criteria. In a number of cases, only single studies have been published to support the use of these agents in patients with bipolar I depression, and therefore the clinical relevance of these data has yet to be determined. The ICG agreed that larger, more robust trials need to be conducted in order to strengthen the evidence base for the use of these treatment options in patients with bipolar I depression.

Divalproex. The classification of divalproex monotherapy as a category 3 agent was derived from the results of an 8-week, double-blind, placebo-controlled, randomized study[45] that evaluated the clinical efficacy of the treatment in 25 outpatients with bipolar I depression. The primary efficacy measure was change in 17-item HAM-D total score from baseline to week 8. Divalproex (up to 2500 mg/day) was significantly more effective than placebo in improving symptoms of depression ($p = .0002$) as shown by reductions in mean HAM-D scores at week 8 from baseline of 43.5% and 27.0% for divalproex and placebo, respectively.[45]

Further evidence is provided by a double-blind, randomized study[46] in which patients with bipolar I depression (N = 18) and patients with bipolar II depression/bipolar depression not otherwise specified (N = 18) received divalproex or placebo for 6 weeks. Divalproex was associated with a significantly greater reduction in MADRS total score, the primary efficacy measure, from baseline to week 6 compared with placebo ($p < .01$; standardized effect size [Cohen d] = 0.81).[46]

Carbamazepine. A double-blind study[47] evaluated the acute effects of carbamazepine monotherapy in 35 patients with depression, including 16 patients with bipolar I depression and 8 with bipolar II depression over a median treatment duration of 45 days. The investigators found that 62% of patients with bipolar depression receiving carbamazepine monotherapy (mean dose of 971 mg/day) experienced a response (mean improvement of ≥ 1 point on the Bunney-Hamburg scale; $p < .001$ vs. baseline).

Fluoxetine. Evidence for the use of fluoxetine as monotherapy for the acute treatment of bipolar depression is provided by the results of a 6-week, double-blind study[48] that compared the efficacy of fluoxetine and imipramine with placebo. Patients with bipolar depression (N = 89) were randomly assigned to fluoxetine (20–80 mg/day, N = 30), imipramine (75–300 mg/day, N = 30), or placebo (N = 29) for 6 weeks, with 22 patients receiving concomitant lithium during the study. Fluoxetine and imipramine were both associated with significant improvement in MADRS total score from baseline to week 6 ($p < .05$ for both treatments) compared with placebo.[48] Furthermore, fluoxetine significantly improved CGI-S score at week 6 compared with imipramine ($p < .05$).

Sertraline and bupropion. The efficacy of sertraline, bupropion, and venlafaxine as adjunctive treatment to mood stabilizers was investigated in a 10-week, randomized, flexible-dose trial[49] in patients with bipolar I depression, bipolar II depression, or bipolar disorder not otherwise specified. All 3 antidepressant treatments were associated with comparable levels of acute response (49%, 51%, and 53% for bupropion, venlafaxine, and sertraline, respectively; defined as a ≥ 50% improvement in Inventory of Depressive Symptomatology [IDS] score or a decrease in Clinical Global Impression-

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Bipolar Disorder [CGI-BP] score of ≥ 2) and remission (34%, 36%, and 41% for venlafaxine, sertraline, and bupropion, respectively; defined as either an IDS score ≤ 12 or a CGI-BP score of 1); however, venlafaxine was associated with a significantly increased risk of switching to hypomania or mania compared with both sertraline and bupropion (29%, 9%, and 10%, respectively; p = .01 venlafaxine vs. sertraline; p < .01 venlafaxine vs. bupropion).[49] Given that there was no placebo group in this study, though, it is not possible to determine if switch rates in the sertraline and bupropion groups were similar to what might be expected over the natural course of the disorder.

Modafinil. Evidence from a recently published double-blind, placebo-controlled, randomized study[50] showed that adjunctive modafinil is an effective treatment for patients with bipolar I depression who respond inadequately to monotherapy with a mood stabilizer. In this study, patients with bipolar I (N = 64) or bipolar II (N = 21) depression were randomly assigned to receive modafinil (200 mg/day) or placebo in combination with a mood stabilizer for 6 weeks. At study endpoint, significant reductions in IDS score (p = .047, effect size = 0.47) and the CGI-BP depression severity item (p = .009, effect size = 0.63) were seen in the modafinil group compared with placebo. Furthermore, response (> 50% improvement in IDS total score) and remission (final IDS total score < 12) rates were significantly higher in the modafinil group compared with placebo (43.9% vs. 22.7% [p < .05] and 39% vs. 18% [p = .033], respectively).[50]

Pramipexole. A 6-week, randomized, placebo-controlled trial[51] investigated the efficacy of pramipexole monotherapy (up to 5 mg/day) in patients with treatment-resistant bipolar I (N = 15) and bipolar II (N = 7) depression. The primary endpoint was response to treatment, defined as > 50% reduction in HAM-D total score. Overall, 67% of patients who received pramipexole responded to treatment compared with 20% of patients who received placebo (p < .05). The change in mean HAM-D scores was greater (p = .05) for pramipexole (48%) compared with placebo (21%). Pramipexole also significantly improved mean CGI-S score from baseline to week 6 compared with placebo (–2.4 and –0.30, respectively; p = .01).[51]

Ethyl-eicosapentaenoic acid. The efficacy of adjunctive ethyl-eicosapentaenoic acid **(**EPA) (1 g/day and 2 g/day) was evaluated in a 12-week randomized, double-blind, placebo-controlled study[52] in 75 patients with bipolar I depression. Both doses of adjunctive EPA (combined data) significantly improved both HAM-D (–3.3 points, 95% CI = –6.1 to –0.2; p < .05; effect size = 0.34) and CGI (–0.79 points, 95% CI = –1.27 to –0.25; p < .05) scores compared with placebo from baseline to the end of the study.

Antidepressants. The ICG agreed that there is little evidence to support the use of antidepressant monotherapy in patients with bipolar disorder, despite their common use.[15] In support of this, results from the McElroy et al. study[35] that investigated the efficacy of quetiapine and paroxetine for the acute treatment of bipolar depression showed that paroxetine did not significantly improve MADRS total scores at week 8 from baseline in patients with bipolar depression (–14.9, paroxetine; –13.4, placebo; p = NS).

The adjunctive use of antidepressants is also a common approach to treatment in bipolar depression. A systematic review and meta-analysis of 5 acute, randomized, double-blind controlled trials (N = 779) compared the use of antidepressants or placebo as adjuncts to a mood stabilizer in patients with bipolar disorder and a current depressive or mixed episode.[53] The authors concluded that antidepressants were a more effective adjunctive therapy than placebo and, moreover, were not associated with a higher incidence of switching to mania.

In some contrast to the Gijsman et al. analysis,[53] the long-term use of adjunctive antidepressants in patients with bipolar I or II depression was evaluated in a large, 26-week, double-blind, randomized, placebo-controlled study (STEP-BD).[54] The primary outcome was durable recovery, defined as euthymia for at least 8 consecutive weeks. Adjunctive treatment with paroxetine or bupropion did not significantly increase the rate of durable recovery compared with the use of mood stabilizers alone (23.5% and 27.3%, respectively; p = .4). Notably, the rate of treatment-emergent affective switch in the 2 groups was not significantly different.[54]

Overall, adjunctive antidepressants may be effective in acute treatment of bipolar I or II depression, but they do not appear to provide any additional benefit in long-term treatment of bipolar depression.

Aripiprazole. To date, there is no clinical evidence to support the efficacy of aripiprazole for the treatment of bipolar I depression.

An analysis of 2 identically designed, 8-week, randomized, double-blind, placebo-controlled studies in patients with bipolar I depression found that aripiprazole (flexible dose of 5–30 mg/day) demonstrated a rapid onset of action (from week 1) with significant reductions in MADRS total score compared with placebo; however, this effect was lost in the final 2 weeks of the trials.[55] Subsequent analysis of data from the 2 trials suggests that the aripiprazole doses used were not adequately determined in advance, leading to high patient withdrawal, which was likely to contribute to the loss of statistical significance toward the end of the trials.[55]

Treatments for the Management of Bipolar II Depression

In contrast to the considerable clinical data available regarding potential treatments for bipolar I depression, there is a relative dearth of clinical evidence from studies in patients with

bipolar II depression.[56] As such, no agents met criteria for category 1 evidence in this setting. This lack of clinical evidence may be a consequence of bipolar I disorder being regarded as a more severe form of illness than bipolar II depression, particularly regarding length and severity of individual depressive episodes[57–59]; however, patients with bipolar II disorder experience a greater frequency of episodes and a longer overall time spent in depression.[8,60]

Category 2 Evidence

Quetiapine. The efficacy of quetiapine monotherapy (300 and 600 mg/day) for the acute treatment of patients with bipolar II depression was evaluated as part of two 8-week, randomized, double-blind, placebo-controlled studies.[33,34] In the bipolar II subgroup of the first study[33] (N = 182), quetiapine monotherapy was associated with a statistically significant improvement in mean MADRS total score at most assessments during the study, compared with placebo. However, the difference in MADRS total score was not significant at final assessment (week 8) with either dose of quetiapine compared with placebo (–14.06, quetiapine 600 mg/day; –14.78, quetiapine 300 mg/day; –12.35, placebo). Effect sizes were 0.39 for quetiapine 600 mg/day and 0.28 for quetiapine 300 mg/day.[33] In the second study,[34] a significant improvement in mean MADRS total score compared with placebo was sustained from week 1 ($p < .05$) to final assessment ($p < .05$) with quetiapine 300 mg/day and from week 3 ($p < .01$) to final assessment ($p < .01$) with quetiapine 600 mg/day in the bipolar II subgroup (N = 152) (Figure 3B).

A post hoc analysis of pooled data from both studies has recently been published and shows that in patients with bipolar II depression, quetiapine monotherapy significantly improved mean MADRS total score from the first assessment (week 1) and at each subsequent assessment.[61] At week 8, mean change from baseline in MADRS total score was –17.1 for quetiapine 300 mg/day ($p < .01$) and –17.9 for quetiapine 600 mg/day ($p < .01$) compared with –13.3 for placebo. Effect sizes were calculated as 0.54 for quetiapine 600 mg/day and 0.45 for quetiapine 300 mg/day.

Additional data regarding the use of quetiapine for the acute treatment of bipolar II depression derive from a randomized, placebo-controlled study that evaluated the acute (8-week) use of quetiapine monotherapy (300 mg/day and 600 mg/day) in this patient group (N = 252).[35] At the end of the study, the investigators reported a mean change in MADRS total score of –16.5 points for quetiapine 300 mg/day, –16.3 points for quetiapine 600 mg/day, and –11.53 points for placebo. Differences in mean MADRS total score were significant for quetiapine 600 mg/day versus placebo (95% CI = –7.93 to –1.67; $p < .05$) and for quetiapine 300 mg/day versus placebo (95% CI = –8.10 to –1.85; $p < .05$). In contrast, the results of a further randomized, placebo-controlled study[19] evaluating the acute (8-week) use of quetiapine monotherapy (300 mg/day and 600 mg/day) in patients with bipolar II depression (N = 296) showed no significant difference in mean MADRS total score from baseline to week 8 for both doses of quetiapine compared with placebo.

Evidence for the long-term use of quetiapine monotherapy in the treatment of bipolar II depression derives from the 26- to 52-week continuation phases of the Young et al.[19] and McElroy et al.[35] studies. As previously noted, quetiapine significantly increased the time to recurrence of depression compared with placebo during the continuation phases of both studies in patients with bipolar I or bipolar II depression.

Category 3 Evidence

Pramipexole. A 6-week, double-blind, placebo-controlled study[62] investigated the efficacy of pramipexole (up to 4.5 mg/day) in patients with bipolar II depression (N = 21). The results of the study revealed a significant treatment effect with pramipexole, as shown by an improvement in total MADRS compared with placebo at week 6 ($p = .03$, 95% CI = 0.104 to 2.27). Furthermore, response (defined as a > 50% decrease in MADRS score from baseline) was experienced by 60% of patients in the pramipexole group compared with 9% in the placebo group ($p = .02$).[62]

Antidepressants. A small, 9-month, randomized, placebo-controlled, crossover study[63] reported significant improvement in depression severity, measured by HAM-D score and percentage of days impaired (effect sizes 1.07 and 0.85, respectively; $p < .05$), in patients with bipolar II disorder (N = 10) receiving selective serotonin reuptake inhibitor (SSRI) monotherapy compared with placebo. However, this study needs to be replicated in a larger sample before any conclusions regarding the efficacy of SSRIs in patients with bipolar II depression can be drawn.

Principles of Treatment for Patients With Bipolar Depression

The principles of treatment for patients with bipolar depression as discussed by the ICG are summarized in Table 3. The ICG suggested that the initial step in the treatment of bipolar depression should be the selection of a suitable first-line (category 1) treatment; however, several factors must be considered on an individual-patient basis when treatment decisions are made, including patient and family history and the tolerability profile of each agent.

The group agreed that optimizing treatment with a first-line pharmacologic agent should be a clinician's next step for patients with bipolar depression. For patients experiencing a lack of response, augmentation of the first-line treatment or a switch to an alternative first-line treatment should be considered. Following this, if response

Table 3. Principles of Treatment for Patients With Bipolar Depression

1. Select first-line treatment (based on the patient's symptom profile, course of illness, prior history of response, family history of response, and tolerability issues)
2. Optimize first-line treatment
3. If no response, augment/switch treatment to another first-line treatment
4. If no response, consider second-line treatments

is not observed, second-line treatments could be initiated.

Special Populations

Further to the general recommendations for the treatment of bipolar depression, the group acknowledged that there are subpopulations of patients with bipolar disorder for whom specific treatment recommendations may be warranted; however, the group agreed that there is a general paucity of evidence in the literature regarding the treatment of these patients.

Rapid Cycling

Lithium and divalproex. A 20-month, double-blind, parallel-group study[64] comparing the efficacy of lithium and divalproex for the long-term treatment of rapid-cycling bipolar disorder has been conducted. Following a 6-month acute stabilization phase, during which patients received open-label lithium and divalproex in combination, 60 patients were randomly assigned to receive lithium monotherapy (mean dose = 1359 mg/day) or divalproex monotherapy (mean dose = 1571 mg/day) for up to 20 months. No statistically significant difference between the lithium and divalproex groups was observed for the primary efficacy measure of time to treatment for a mood episode.

Lamotrigine. The use of lamotrigine as a maintenance treatment in rapid-cycling bipolar disorder was investigated in a double-blind, placebo-controlled, prophylaxis study.[65] Patients (N = 324) received lamotrigine or placebo as monotherapy for 6 months following a preliminary, open-label stabilization phase. The primary efficacy measure was time to additional pharmacotherapy for emerging mood symptoms. No significant difference between the lamotrigine and placebo groups with respect to the primary measure was observed. However, lamotrigine was associated with a significantly greater time to premature discontinuation compared with placebo ($p < .05$). Furthermore, significantly more patients receiving lamotrigine (41%) were stable without relapse for the duration of the study compared with placebo (26%; $p < .05$).[65]

Quetiapine. Evidence for the use of quetiapine monotherapy in patients with a rapid-cycling disease course has been provided by a subanalysis of an 8-week, randomized, double-blind, placebo-controlled study.[33] Quetiapine (600 and 300 mg/day) provided significantly greater mean reductions from baseline to week 8 in MADRS total score than placebo ($p < .001$ for both doses) in patients with a rapid-cycling disease course. Effect sizes in patients with rapid cycling were 1.2 (600 mg/day) and 1.1 (300 mg/day). Moreover, effect sizes were 0.98 and 1.22, respectively, for the bipolar I subgroup and 1.45 and 0.97, respectively, for the bipolar II subgroup.[66]

Antidepressants. A 10-week, randomized, flexible-dose study[49] evaluating sertraline, bupropion, and venlafaxine as adjuncts to mood stabilizers investigated the impact of a patient's rapid cycling status on the relative risk of switching into mania or hypomania. In patients without rapid cycling, the risk of switching was no different with the 3 study medications ($p = .55$); however, in patients with a rapid-cycling disease course, bupropion was associated with a significantly lower risk of switching than venlafaxine ($p < .01$).

Pregnancy and Lactation

Substantial gaps remain in our knowledge of the course, risk factors, and treatment effects among women with bipolar disorder during pregnancy.[67,68] Some studies suggest that pregnancy may be protective against risk of recurrence[69,70]; however, other reports, some of which are more recent, suggest that pregnancy carries a high risk for new morbidity in women with bipolar disorder, and most of the morbidity appears to be due to depressive and dysphoric states.[71–75]

In 2004, under the aegis of the American Psychiatric Association, a consensus panel of experts in the field published treatment guidelines for the management of bipolar disorder during pregnancy and lactation.[76] To date, no specific controlled treatment trials in pregnancy have been conducted, most likely due to the inherent difficulties and ethical challenges in randomly assigning pregnant women to a specific treatment group. However, recent studies have begun to quantify risk of recurrence associated with continuation or discontinuation of maintenance mood-stabilizer treatment during pregnancy. In one retrospective study[74] of women with bipolar disorder, lithium discontinuation carried a high risk of illness recurrence during pregnancy of around 52%. More recently, prospective studies have demonstrated that discontinuation of prophylactic mood-stabilizing treatment, particularly abruptly, carries an even higher risk of illness recurrence than previously estimated, with risk estimated at around 85% in one study[73] and 100% in another study involving lamotrigine discontinuation.[77] However, in both studies, continuation of mood-stabilizer treatment during pregnancy was associated with a substantial 2-fold reduction in recurrence risk as well as a substantial 5-fold reduction in total time spent in an illness episode.[73,77]

A critical and urgent question is how best to treat women with bipolar disorder during pregnancy, especially those patients at particularly high risk for bipolar-depressive and dysphoric mixed states. Mood-stabilizing treatments for bipolar disorder appear to be of substantial value in pregnancy, but they are associated with variable risks

of fetal teratogenic outcomes. Lithium is one of the oldest known teratogens associated with an increased risk for a specific congenital heart malformation, Ebstein's anomaly. While initial reports suggested a 400-fold increased risk of this anomaly following first trimester exposure to lithium, a subsequent meta-analysis of more recent, controlled epidemiologic studies, estimated a substantially lower relative risk of 10 to 20 times the baseline risk in the general population (1/20,000), with an absolute risk ranging between 1/1000 to 1/2000 exposed infants.[78]

Among the commonly used anticonvulsants, emerging and compelling data from several pregnancy registries and studies suggest a differential teratogenic risk.[79–81] The majority of evidence to date suggests that divalproex is associated with the highest risk for all major malformations (including cardiac malformations, oral clefts, urologic defects, skeletal defects, and neural tube defects), with risk estimates in the range of 10% to 16%, representing a 2- to 3-fold increased risk compared with lamotrigine and carbamazepine.[79,80,82] Data also suggest that treatment combinations that include divalproex carry a higher risk of major malformations than those without divalproex.[79,80,83] Risk of malformations appears to increase in a dose-dependent fashion, with higher rates of malformations at doses above approximately 1000 mg/day.[79,80,84,85] In addition, several retrospective and small prospective studies suggest that divalproex exposure is associated with an increased risk for behavioral teratogenesis.[84–88] Children exposed to divalproex are more likely to experience developmental delays, have a lower verbal IQ, and have an increased need for special education services compared with children exposed to other anticonvulsants.[84–87] However, further prospective, longitudinal studies are needed to assess behavioral teratogenesis across all anticonvulsants, especially the second-generation compounds. Given these concerns regarding divalproex use in pregnancy, there is a growing consensus that divalproex should not be considered as a first-line treatment option in women of childbearing age,[79,88–90] but should be used only when clinical circumstances dictate no other treatment alternative.

Among the newer anticonvulsants, lamotrigine has the most reproductive safety information available, and the majority of data do not suggest an increased risk for all major malformations above the baseline risk.[79,80,91] Whether there is a positive dose response for major malformations with lamotrigine exposure remains controversial.[83,92] However, recent unpublished, preliminary data from the North American Pregnancy Registry suggest that lamotrigine may be associated with an increased risk for a specific malformation, oral clefts (including cleft lip and/or palate), with an incidence of 8.9/1000 compared with 0.16–0.21/1000 in the comparison group.[93] While other registries have not corroborated this finding to date, further data are needed in order to make any definitive assessment of risk for specific malformations associated with lamotrigine or other anticonvulsants, or to define whether a dose-response relationship exists across the newer anticonvulsants.

Although the atypical antipsychotics have been available since the mid-1990s and are widely used by women with bipolar disorder of reproductive age, data regarding the reproductive safety of these compounds are limited to case reports and manufacturers' postmarketing data. In one prospective, comparative study of pregnancy outcomes between groups exposed and unexposed to atypical antipsychotics, outcomes of 151 pregnancies with exposure to olanzapine, risperidone, quetiapine, and clozapine suggested no increased risk of congenital malformations.[94–96] Thus far, the available data do not suggest a specific pattern of malformations, but further prospective, controlled studies are needed, as well as long-term neurobehavioral outcomes, before any definitive conclusions may be made regarding the reproductive safety of this class of compounds.[94–96]

With regard to the postpartum period, the literature consistently describes the first few months as a period of heightened vulnerability to relapse of mood disorders, especially for women with bipolar disorder.[67,76,97] Three open-label trials (combined N = 65) demonstrate substantial benefit of lithium prophylaxis in reducing recurrence risk by nearly 5-fold.[98–100] Later investigations examining the efficacy of other agents, including hormonal interventions, for postpartum prophylaxis have been mixed.[101–104]

There has also been considerable debate regarding the relative safety of psychotropic medications during lactation and the optimal means for determining nursing infant exposure.[90,105] Data regarding excretion into human breast milk and effects of nursing infant exposure for most of the mood stabilizers are limited by small sample sizes. All psychotropic medications enter breast milk, although medication exposure for the nursing infant is considerably less than placental transfer; specifically, for lithium, divalproex, and lamotrigine, the placental passage ratio approaches approximately 1:1.[77,105,106] Most of the mood stabilizers and atypical antipsychotics are found in low to very low levels in the nursing infant and do not appear to have an adverse effect on infant well-being.[77,105–109] Recent studies based on a combined sample size of approximately 40 infants demonstrated that levels of lamotrigine (total concentrations) and lithium in nursing infants are approximately 18% and 24% of maternal serum levels, respectively, and drug exposure was not associated with any clinically significant adverse events.[75,109] Despite the absence of treatment-emergent adverse events in these studies, investigators caution that breastfeeding while receiving mood stabilizers is appropriate for only a highly selected group of women with bipolar disorder. Suitable clinical characteristics include (1) stable maternal mood; (2) drug monotherapy, or at

least a simple medication regimen; (3) patient compliance with infant monitoring recommendations; (4) a healthy, term infant; and (5) a collaborative pediatrician.[109] Further studies assessing larger cohorts of nursing infants are needed to quantify exposure to all mood stabilizers during lactation and to examine the spectrum of possible adverse effects, as well as to define optimal monitoring requirements.[75,90,105,109]

The summary of the above findings is a first step in providing data-driven recommendations for the clinical management of pregnant women with bipolar disorder. The safety of treating bipolar disorder during pregnancy can be improved with close clinical monitoring, prepregnancy treatment planning, and due consideration to the spectrum of risks and benefits associated with either pursuing or deferring treatment with psychiatric medications during pregnancy.

Other Populations

The ICG identified additional groups of patients who may require particular treatment recommendations for the management of bipolar disorder; however, the group acknowledged that there are no specific, controlled trials in bipolar depression in these subpopulations of patients.

- Dual-diagnosis bipolar disorder
- Older adults
- Children and adolescents

Recommendations for Future Clinical Research

The ICG members concluded that future clinical research should address the short- and long-term treatment of bipolar depression by evaluating meaningful endpoints, including not only standard depression rating scales but also measures of anxiety, subthreshold manic symptoms, and functional outcome.

Specific trials should be devoted to patients with bipolar II disorder, children and adolescents, older adults, patients with rapid cycling, and patients with comorbidities, such as substance abuse. Trials clarifying the role (if any) of antidepressants and evaluating the efficacy of novel antipsychotic, anticonvulsant, or antidepressant compounds in bipolar depression would be of particular interest.

Potentially exciting novel mechanisms of action should be explored in order to expand the treatment options beyond those available. Head-to-head studies, particularly of those compounds classified in these recommendations as category 1, should be conducted. Furthermore, combinations of 2 or more drugs should also be evaluated, as combination therapy is currently the rule in clinical practice rather than the exception. Predictors of response to particular drugs and the potential antisuicidal effects of some compounds should also be further explored (see Table 4 for a summary of these recommendations).

Table 4. Recommendations for Future Research

Studies in patients with bipolar II depression (acute and long-term treatment)
Studies in patients with bipolar depression and comorbid substance abuse
Studies in patients with bipolar depression with a rapid-cycling course
Studies in children, adolescents, and older adults
Placebo-controlled trials of acute and long-term antidepressant use
Comparative (head-to-head) studies of lithium vs lamotrigine vs quetiapine
Studies of specific combinations of pharmacologic treatments
Studies of predictors of response to individual agents
Large studies on the prevention of suicide

Drug names: aripiprazole (Abilify), bupropion (Wellbutrin, Aplenzin, and others), carbamazepine (Carbatrol, Equetro, and others), clozapine (FazaClo, Clozaril, and others), divalproex (Depakote), fluoxetine (Prozac and others), imipramine (Tofranil and others), lamotrigine (Lamictal and others), lithium (Eskalith, Lithobid, and others), modafinil (Provigil), olanzapine (Zyprexa), olanzapine/fluoxetine combination (Symbyax), paroxetine (Paxil, Pexeva, and others), pramipexole (Mirapex and others), quetiapine (Seroquel), risperidone (Risperdal), sertraline (Zoloft and others), venlafaxine (Effexor and others).

Disclosure of off-label usage: The chair has determined that, to the best of his knowledge, aripiprazole, bupropion, carbamazepine, divalproex, fluoxetine, imipramine, inositol, lithium, modafinil, olanzapine, paroxetine, pramipexole, risperidone, sertraline, and venlafaxine are not approved by the U.S. Food and Drug Administration for the treatment of bipolar depression; lamotrigine is not approved for the acute treatment of bipolar depression; the olanzapine/fluoxetine combination is not approved for the long-term treatment of bipolar depression; and quetiapine is not approved for long-term monotherapy treatment of bipolar depression.

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For the CME Posttest for this ACADEMIC HIGHLIGHTS, see pages 1666–1667.

