International Consensus Group on Depression Prevention in Bipolar Disorder

On February 28, 2011, Mark A. Frye, MD, assembled a group of international experts to review the evidence base for treatments for bipolar depression, discuss standards of care, and outline a universal treatment algorithm for the prevention of and maintenance treatment of bipolar depression. This COMMENTARY section of *The Journal of Clinical Psychiatry* presents the highlights of their discussion.

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Bipolar disorder is a serious and debilitating illness associated with considerable functional impairment, comorbidity, and suicidality.[1] Although bipolar disorder is defined by the presence of mania or hypomania, patients typically spend a greater amount of time depressed than manic.[2] Depressive episodes in bipolar disorder are associated with greater symptom severity and cause greater role impairment than manic or hypomanic episodes. However, despite the availability of treatments approved by the US Food and Drug Administration (FDA), many patients treated for bipolar depression do not receive optimal medications as part of their regimen.

Mark A. Frye, MD, assembled an international group of experts in psychiatry to review the evidence base for depression prevention treatment in patients with bipolar disorder and formulate a consensus treatment strategy. Topics addressed by the group included the evolution of trial design, adverse events of treatment and medical comorbidities associated with bipolar disorder, antidepressant use in bipolar treatment, and the standards of care for bipolar depression prevention in Japan, Korea, Turkey, and Argentina.

EVIDENCE BASE FOR STRATEGIES FOR PREVENTING DEPRESSION IN BIPOLAR DISORDER

Dr Frye began by reviewing the evidence base of the 7 medications approved by the FDA as maintenance treatment for bipolar disorder. The evidence base, in turn, illustrates the evolution of trial design in relation to maintenance therapy in bipolar depression and the impact this evolution has made on the clinical relevance of outcome measures.

The core components of maintenance studies in bipolar disorder are the screening phase, stabilization phase, and recurrence assessment (randomization) phase (Figure 1).[3] Although screening and stabilization phase criteria may set the stage for how clinically important the outcome measure of the randomization phase will be, historically, screening criteria and the method of stabilizing patients, the definition of stabilization, and the length of stabilization phases have varied across studies. Researchers are coming to accept the need for a cross-study consensus on the screening criteria and duration of stabilization phases to make the results of outcome measurements more consistent. More comparable trial results would help to standardize the wording of FDA indications and aid in the development of algorithms.

Pharmacotherapy Trials

Lamotrigine and lithium. Dr Frye reviewed an 18-month study by Goodwin et al,[4] which found that both lamotrigine monotherapy and lithium monotherapy increased time to intervention for a manic, hypomanic, or mixed episode compared with placebo. However, only lamotrigine was superior to placebo in time to intervention for a depressive episode ($P = .009$).

In this and the following regulatory studies, all subjects had bipolar I disorder. Patients in this study were currently or recently manic, hypomanic, depressed, or in mixed states. The stabilization phase of the study lasted 8 to 16 weeks, and those who met response criteria for at least 4 consecutive weeks entered the recurrence assessment phase (N = 638). During the stabilization phase, all patients were given lamotrigine, while other psychotropic medications that patients may have been receiving were tapered.

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For Clinical Use

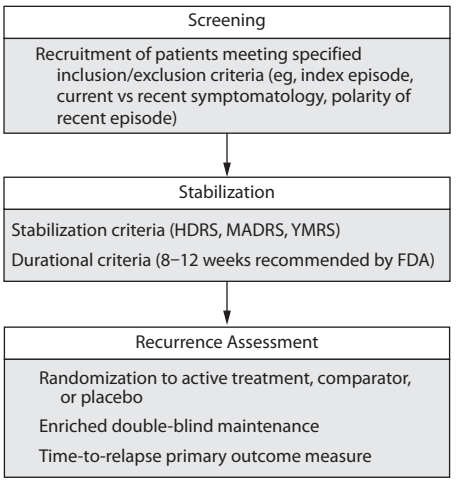
- Lamotrigine and quetiapine have the best evidence base for preventing bipolar depressive episodes.
- Antidepressant monotherapy is not recommended for acute or maintenance treatment of bipolar depression.
- When choosing treatments, take into consideration the patient's comorbidities and course of illness (eg, rapid cycling, predominant polarity, history of relapse) and the adverse effect profiles of each medication.

Olanzapine. Tohen et al[5] evaluated the efficacy of olanzapine monotherapy as maintenance therapy for up to 48 weeks. Patients with manic or mixed episodes received acute treatment with olanzapine for 6 to 12 weeks; those who met remission criteria for at least 2 consecutive weeks entered the randomization phase (N = 361). Time to relapse into any mood episode was significantly longer with olanzapine than placebo ($P < .001$), and the overall relapse rates at study endpoint were 47% for olanzapine versus 80% for placebo. Secondary analyses identified relapse rates for both mania and depression were significantly reduced with olanzapine. Dr Frye pointed out that the study design, specifically the brief remission criteria of 2 weeks, may have contributed to the rapid rate of relapse at the start of the randomization phase, demonstrating the clinical importance of the length of stabilization phases in maintenance trials.

Aripiprazole. Dr Frye then described a study[6] designed to evaluate the efficacy of aripiprazole monotherapy as bipolar maintenance treatment. Patients who recently had manic or mixed episodes were stabilized with aripiprazole over 6 to 18 weeks, and those who were stable for 4 consecutive weeks were randomly assigned to receive either aripiprazole or placebo for 26 weeks (N = 161). Patients in the aripiprazole group experienced a longer time to relapse into manic episodes ($P = .01$) and had fewer relapses ($P = .013$) compared with those in the placebo group. However, aripiprazole did not provide a significant difference in time to intervention for a depressive episode compared with placebo. Dr Frye commented that to fully evaluate aripiprazole in depression maintenance, the study would have needed to include patients presenting with a depressive episode.

Quetiapine. There are no controlled studies of quetiapine monotherapy as maintenance therapy. A 2-year study[7] of patients with a recent manic, depressive, or mixed episode had an open-label phase of up to 36 weeks, and patients had to achieve stability for at least 12 weeks using a combination of quetiapine and lithium or divalproex to enter randomization (N = 703). Those taking quetiapine plus lithium or divalproex had a significantly longer time to recurrence for both manic and depressive episodes compared with the group taking placebo plus lithium or divalproex ($P < .001$ for both). The polarity of the index episode had no effect on recurrence.

Figure 1. Core Components of Maintenance Treatment Studies[a]



[a]Data from Gitlin et al.[3]
Abbreviations: FDA = US Food and Drug Administration, HDRS = Hamilton Depression Rating Scale, MADRS = Montgomery-Asberg Depression Rating Scale, YMRS = Young Mania Rating Scale.

Ziprasidone. There are controlled studies of ziprasidone monotherapy as maintenance therapy. A 6-month study[8] of ziprasidone as an adjunct to lithium or valproate found a significant benefit for ziprasidone plus mood stabilizer in time to manic or mixed relapse when compared with adjunctive placebo ($P = .0035$), but no significant benefit was found for the ziprasidone group in time to depressive relapse. The inclusion criteria of the screening phase required patients to have a recent or current manic or mixed episode; patients received ziprasidone plus a mood stabilizer for 16 weeks, with those being stable for 8 consecutive weeks entering the recurrence assessment phase (N = 240).

Risperidone. A long-acting injectable formulation of risperidone is indicated for maintenance treatment of bipolar I disorder both as monotherapy[9] and as adjunctive pharmacotherapy.[10] Like lithium, aripiprazole, and ziprasidone, risperidone appears to be effective in antimanic prophylaxis but not significantly more effective than placebo in reducing time to depressive relapse. In the monotherapy study,[9] patients with recent manic or mixed episodes who maintained response to risperidone for 26 weeks were randomly assigned to the 24-month recurrence assessment phase (N = 303). In the smaller adjunctive treatment study,[10] the patients enrolled were those who frequently relapsed (N = 124) and sample size did not allow secondary analyses of depression relapses specifically.

Nonregulatory studies. Dr Frye explained that nonregulatory studies can be more easily translated into clinical practice than regulatory studies, since they may not have the inclusion and exclusion criteria that often limit the generalizability of regulatory studies to community samples. For example, in the BALANCE (Bipolar Affective disorder: Lithium/ANti-Convulsant Evaluation) trial,[11] 8% of

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the cohort had active substance or alcohol abuse, and this subgroup typically would be excluded in regulatory studies. In the 4- to 8-week stabilization phase of the BALANCE trial, patients received combined lithium and valproate. In the 2-year recurrence assessment phase, patients received lithium, valproate, or the combination (N = 330). Treatment with combination therapy and lithium monotherapy significantly reduced risk of recurrence compared with valproate monotherapy ($P < .05$ for both), and the benefit was maintained for up to 2 years. The benefit of combination therapy over valproate monotherapy was primarily due to mania prophylaxis, while the benefit of lithium monotherapy over valproate monotherapy was primarily due to depression prophylaxis. Combination therapy did not produce a significant benefit compared with lithium monotherapy.

Another nonregulatory trial[12] was a long-term follow-up of responders to lithium plus lamotrigine in 8-week acute phase treatment.[13] In that study, patients had either bipolar I or II disorder and experienced a depressive episode while taking lithium monotherapy (N = 124). Compared with lithium plus placebo, lithium plus lamotrigine not only was more effective in the acute treatment of bipolar depression but also retained its advantage during the follow-up phase. Median time to relapse for the group receiving lamotrigine was 10 months versus the placebo duration of 3.5 months.

Psychosocial interventions. In addition to pharmacotherapy, adjunctive psychosocial interventions have demonstrated efficacy in improving the likelihood of remaining well after stabilization of a bipolar depressive episode. Miklowitz et al[14] compared intensive psychotherapy interventions with collaborative care in patients also receiving pharmacotherapy (N = 293). Patients receiving intensive psychotherapy had a 58% greater likelihood of being clinically well during any month of follow-up than those who received collaborative care ($P = .003$). All intensive psychotherapies were associated with higher recovery rates and a shorter period of time to recovery than collaborative care. Dr Frye commented that the efficacy of these structured psychotherapies is impressive; the imperative is increasing access to these providers and treatment.

Subsyndromal symptoms. Dr Frye observed that, in most of the previously mentioned studies, time to intervention for a mood episode (syndromal recurrence) was the primary outcome measure. However, subsyndromal depressive symptoms during bipolar maintenance treatment are common, are associated with impaired functioning at work, at home, and in relationships with family and friends,[15] and are predictive of depressive relapse.[16] So, while a study's outcome measure may be time to syndromal relapse, clinicians can achieve a better clinical outcome by vigilantly screening for subsyndromal symptoms and making appropriate changes to a treatment regimen should they develop.

Conclusion

Dr Frye pointed out that screening, stabilization, relapse, and recurrence criteria have varied in trials of bipolar depression maintenance treatments, but that as trial design has evolved and stabilization criteria have increased, higher rates of completion have been seen in the maintenance phase of bipolar studies.

Seven treatments have FDA approval for use in bipolar maintenance, with lamotrigine, olanzapine, and adjunctive quetiapine having the strongest data showing depression prophylaxis. Psychosocial interventions also yield maintenance benefits when used as an adjunct to pharmacotherapy. Dr Frye concluded that optimal recovery in the maintenance phase of bipolar disorder—particularly depression prophylaxis—requires multimodal combination treatments, careful monitoring for subsyndromal symptoms, and vigilance for treatment-emergent side effects.

ADVERSE EVENTS AND MEDICAL COMORBIDITIES ASSOCIATED WITH BIPOLAR DISORDER

Susan L. McElroy, MD, discussed medical comorbidities and treatment-related adverse events associated with bipolar disorder. A bidirectional relationship appears to exist between depression and medical illness in patients with bipolar disorder. By minimizing the occurrence of depressive episodes, clinicians may prevent some medical burden, and vice versa. Clinicians can also minimize medical burden and perhaps decrease the occurrence of depressive episodes by managing treatment-related adverse events.

General Medical Condition Comorbidities

Dr McElroy pointed out that, compared with the general population, patients with bipolar disorder have elevated mortality rates not only from unnatural causes, such as suicide, but also from natural causes.[17] Individuals with bipolar disorder are at increased risk for multiple general medical conditions (GMCs) across almost all organ systems compared with those without bipolar disorder ($P < .0001$).[18]

Data from the National Epidemiologic Survey on Alcohol and Related Conditions[19] (NESARC) showed that, compared with adults without bipolar I disorder, adults with bipolar I disorder had a significantly elevated risk of 8 of the 11 medical conditions examined (Table 1), some of which were especially associated with bipolar depression (arthritis, angina, tachycardia, and stomach ulcers). The NESARC data[20] also showed that not only do individuals with bipolar disorder have more medical illness than those without the disorder, they are sick earlier; for example, the mean ages of patients with bipolar disorder who had cardiovascular disease or hypertension were, respectively, 14 and 13 years younger than those who did not have bipolar disorder.

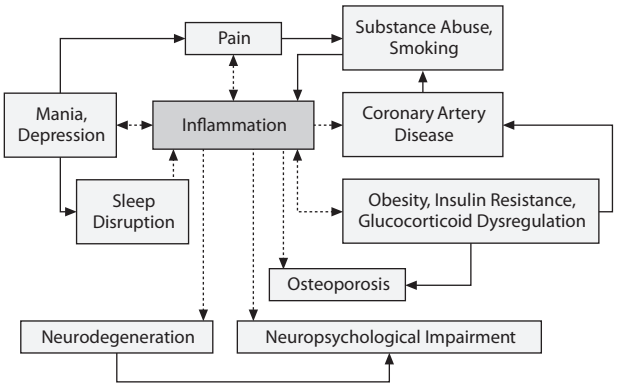
Baseline depressive severity in patients with rapid-cycling bipolar I or II disorder has been reported to have a positive relationship with the number of organ systems affected by GMCs ($P = .04$).[21] An inverse correlation has also been found between endocrine/metabolic illnesses, particularly obesity, and depressive remission ($P = .02$).

Table 1. Annual Prevalence Rates of GMCs Among Adults With and Without Bipolar I Disorder and Lifetime History of a Major Depressive Episode[a]

	Overall Sample Comparison			Subsample Comparison		
Variable	Adults Without Bipolar I Disorder (n = 41,545), % (SE)	Adults With Bipolar I Disorder (n = 1,548), % (SE)	χ^2	Adults With Bipolar I Disorder Without Major Depressive Episode (n = 451), % (SE)	Adults With Bipolar I Disorder and Major Depressive Episode (n = 1,097), % (SE)	χ^2
Arthritis	20.92 (0.52)	30.73 (1.54)	34.14***	21.89 (2.38)	34.32 (1.80)	16.91***
Hypertension	18.99 (0.39)	24.34 (1.50)	11.37**	21.25 (2.60)	25.60 (1.80)	1.87
Gastritis	5.93 (0.17)	14.99 (1.07)	45.83***	12.45 (2.12)	16.02 (1.28)	1.92
Angina	5.73 (0.17)	17.94 (1.32)	50.43***	13.34 (1.89)	19.81 (1.63)	6.84*
Tachycardia	5.70 (0.17)	17.88 (1.34)	57.79***	11.61 (1.84)	20.43 (1.73)	10.72**
Other forms of heart disease[b]	2.80 (0.12)	4.24 (0.62)	5.40*	3.24 (1.09)	4.64 (0.73)	1.17
Stomach ulcer	2.50 (0.10)	9.11 (0.87)	48.33***	6.29 (1.55)	10.25 (1.04)	4.32*
Arteriosclerosis	1.89 (0.09)	2.68 (0.48)	2.74	2.48 (0.95)	2.77 (0.57)	0.06
Myocardial infarction	.93 (0.06)	1.19 (0.28)	0.83	1.00 (0.44)	1.27 (0.34)	0.25
Other forms of liver disease[b]	.53 (0.04)	1.95 (0.41)	11.81***	1.40 (0.61)	2.18 (0.53)	0.89
Cirrhosis of the liver	.21 (0.03)	.91 (0.38)	3.20	0.55 (0.39)	1.06 (0.50)	0.65

[a]Reprinted with permission from Perron et al.[19]
[b]Refers to generic categories included in the original NESARC survey and includes all forms of heart and liver disease other than those specifically assessed.
*P < .05. **P < .01. ***P < .001.
Abbreviations: GMC = general medical condition, NESARC = National Epidemiologic Survey on Alcohol and Related Conditions.

Figure 2. Putative Role of Inflammation in Bipolar Disorder[a]



[a]Reprinted with permission from Goldstein et al.[20]

Reasons for Increased GMCs in Individuals With Bipolar Disorder

The relationship between bipolar disorder and its associated medical comorbidities is not well understood, but potential reasons for the increased general medical burden in patients with bipolar disorder are numerous and varied. Some comorbid conditions may be related to lifestyle behaviors. For example, individuals with bipolar disorder engage in high-risk behaviors that are known to contribute to medical conditions, such as substance abuse, nicotine use, and unsafe sex.[20] People with bipolar disorder often have poor diets, reduced physical activity, and increased obesity, and they tend to have lower education, which may contribute to reduced awareness of health needs. Additionally, psychotropic medication side effects may contribute to the general medical burden of bipolar disorder.

Dr McElroy noted that bipolar disorder may also share a common pathophysiology with a number of the GMCs with which it occurs. For instance, inflammation may play a role in the etiology of bipolar disorder and a number of conditions that co-occur with bipolar disorder (Figure 2).[20] Some study data[22] suggest that the mechanism of action of mood stabilizers may include an anti-inflammatory process. Conversely, some proven anti-inflammatory treatments, such as statins[23] and omega-3 fatty acids,[24] may have antidepressant properties.

Treatment-Related Adverse Events

Dr McElroy stated that medical comorbidities and medication-related adverse events may overlap, and the interactions between them need to be monitored. For example, metabolic issues may arise with certain treatments, in addition to the already elevated risk for obesity and diabetes among individuals with bipolar disorder.[25] Obesity not only affects morbidity and mortality related to physical illness but is correlated with a greater risk for depressive recurrence in patients with bipolar disorder.[26]

Atypical antipsychotics have marked differences in their effects on weight and metabolic measures (eg, triglyceride levels). Studies[27–29] have shown that olanzapine and clozapine are associated with the most weight gain and metabolic side effects in the class, while aripiprazole and ziprasidone are associated with the least.

A study[30] comparing lamotrigine and lithium in obese and no obese patients with bipolar I disorder found that, for no obese patients, neither agent had a significant effect on weight. However, for patients who were obese at baseline, treatment with lithium was associated with weight gain, while the lamotrigine group experienced weight loss.

For some patients, initially choosing or switching to a medication not associated with weight gain may be enough to avoid iatrogenic metabolic issues. However, noted Dr McElroy, for patients in whom weight-gain–inducing agents are necessary, diet modifications and moderate physical activity have been to shown to reduce weight gain caused by

atypical antipsychotics.[31] In addition, certain medications, such as metformin, may reduce or prevent weight gain.[32]

Hypothyroidism, which is associated with depression, is another common comorbidity of bipolar disorder.[18] A study[33] demonstrated that, even within the normal range of thyroid function, individuals with higher levels of thyroid-stimulating hormone (TSH) experienced slower response to treatment than those with lower levels. Lithium treatment, breakthrough depression, and higher TSH levels all co-occurred in one study,[34] a constellation of events that was not seen in the groups receiving lamotrigine or placebo. Dr McElroy advised that clinicians should be aware of the standards for evaluating and treating hypothyroidism published by the American Association of Clinical Endocrinologists, which suggest that optimal levels of TSH are between 0.3 and 3.0 μIU/mL.[35]

Conclusion

Dr McElroy stressed the importance of assessing and monitoring bipolar patients for comorbid GMCs, working with primary care providers and specialists to develop treatment programs for individual patients, and choosing medications with optimal efficacy and low risk of adverse events. Clinicians can prevent or address weight gain with education about proper nutrition and exercise, weight-neutral medications, and weight-reducing medications when necessary. They should also consider managing certain medical comorbidities with compounds that may have antidepressant properties, such as stations and omega-3 fatty acids. Thyroid function should be monitored as well.

USE OF ANTIDEPRESSANTS IN BIPOLAR DEPRESSION

Antidepressants are the most commonly prescribed initial treatment in the United States for patients with bipolar disorder, despite treatment guidelines recommending against their use as monotherapy.[36,37] Eduard Vieta, MD, PhD, examined the evidence base in regards to the common but controversial use of antidepressants in bipolar disorder.

Evidence Base for Antidepressant Treatment

Antidepressant monotherapy. Dr Vieta first reviewed one of the few studies[38] that assessed antidepressant monotherapy in bipolar depression, which compared quetiapine (300 and 600 mg/d) and paroxetine with placebo for 8 weeks. Paroxetine was not more effective than placebo, but both doses of quetiapine were. Another study,[39] which compared the clinical courses of patients followed for a mean of 10 years, found that those who initially received antidepressant monotherapy for an index episode had a higher rate of switching to mania or hypomania and of attempted suicide than those who initially received an antidepressant combined with a mood stabilizer. Dr Vieta interpreted these results to mean that mood stabilizers protect against switching, and lithium in particular might protect against attempted suicide, rather than that antidepressants necessarily induce mood switches or suicide attempts.

Adjunctive antidepressant treatment. Dr Vieta next described studies of adjunctive use of antidepressants, which have had mixed results. In a STEP-BD study[40] of patients with bipolar depression treated with a mood stabilizer, the use of adjunctive bupropion or paroxetine for up to 26 weeks provided no clear benefit. No differences in efficacy, durable recovery, or switch rates were associated with adjunctive antidepressant versus adjunctive placebo.

In contrast, another trial[41] reported that patients with bipolar depression taking mood stabilizers improved with an adjunctive selective serotonin reuptake inhibitor (SSRI; paroxetine) or serotonin-norepinephrine reuptake inhibitor (SNRI; venlafaxine), although the study had no placebo control. However, the likelihood of mood switch was greater with the SNRI (13%) than with the SSRI (3%). This result was corroborated by a study[42] in which adjunctive venlafaxine was associated with increased risk of mood switch compared with adjunctive bupropion or sertraline. Dr Vieta added that tricyclic antidepressants (TCAs) also seem to carry an increased risk of mood switch compared with SSRIs, and limited data suggest that cycle acceleration may occur.[43]

The strongest evidence supporting adjunctive antidepressant use in bipolar disorder is for fluoxetine. In an 8-week study by Tohen et al,[44] the efficacy of olanzapine monotherapy and olanzapine combined with fluoxetine versus placebo was examined in patients with bipolar I depression. The addition of fluoxetine provided a significant benefit over olanzapine alone ($P < .02$), as well as over placebo ($P < .001$).

Predictors of response to adjunctive antidepressants were examined by Dr Vieta and colleagues in a naturalistic study.[45] The most powerful predictor of response was previous response to antidepressants. A greater number of mood switches during prior antidepressant treatment was a predictor of nonresponse. Nonresponders also had more previous total, depressive, and hypomanic (but not manic or mixed) episodes than responders.

Treatment-resistant bipolar depression. Dr Vieta and colleagues (Pacchiarotti et al[46,47]) have proposed a treatment algorithm to establish the severity of treatment resistance in a patient with bipolar depression. The first level is failure to reach remission with first-line treatment (either an adequately dosed mood stabilizer plus lamotrigine or adequately dosed quetiapine monotherapy). Patients at this level of treatment resistance can switch to the other first-line treatment or progress to the next treatment step, in which antidepressants may play a role.

Adding an antidepressant in treatment-resistant bipolar disorder was examined in the LamLit study.[13] The first phase of the study supported the use of lithium plus lamotrigine versus lithium plus placebo in patients with bipolar disorder in a depressive episode despite treatment with lithium alone. In the 8-week second phase,[14] paroxetine had a positive effect in nonresponders taking lithium plus placebo but not in nonresponders taking lithium plus lamotrigine;

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Table 2. Rates of New Depression or Mania in Trials Comparing Antidepressants With and Without a Mood Stabilizer Versus a Mood Stabilizer or Placebo[a]

	Treatment Group		Rate of New Episode, Relative Risk (95% CI)	
Study	Antidepressant	Control	Depression	Mania
Prien et al[51] 1973	Imipramine	Placebo	0.40 (0.17–0.95)	1.60 (0.71–3.60)
Prien et al[51] 1973	Imipramine	Lithium	0.92 (0.32–2.62)	5.54 (1.40–21.9)
Quitkin et al[52] 1981	Imipramine + lithium	Lithium	0.77 (0.18–3.21)	2.31 (0.78–6.85)
Kane et al[53] 1982	Imipramine	Placebo	0.70 (0.20–2.44)	1.40 (0.11–17.5)
Kane et al[53] 1982	Imipramine	Lithium	1.60 (0.21–11.9)	2.50 (0.13–48.8)
Kane et al[53] 1982	Imipramine + lithium	Placebo	0.29 (0.04–1.95)	0.38 (0.02–7.93)
Kane et al[53] 1982	Imipramine + lithium	Lithium	0.67 (0.06–7.85)	Not provided
Prien et al[54] 1984	Imipramine	Lithium	0.97 (0.48–1.98)	2.02 (1.11–3.65)
Prien et al[54] 1984	Imipramine + lithium	Lithium	0.78 (0.36–1.69)	1.06 (0.51–2.20)
Johnstone et al[55] 1990	Amitriptyline + lithium	Lithium	1.60 (0.51–5.03)	Not provided
Amsterdam et al[56] 2005	Fluoxetine	Placebo	0.38 (0.15–0.92)	Not provided
Ghaemi et al[57] 2005	Antidepressants + mood stabilizers	Mood stabilizers	0.77 (0.42–1.39)	1.42 (0.48–4.24)
Totals	Antidepressants ± mood stabilizers	Mood stabilizer or placebo	0.726 (0.547–0.962)	1.72 (1.23–2.41)

[a]Data from Ghaemi et al.[50]

at endpoint, no significant difference existed between the lithium plus paroxetine group and the lithium plus lamotrigine group.

Antidepressant use in manic episodes. The evidence base suggests that an antidepressant should not be added if the patient has any manic symptoms because the risk of a manic switch is greater.[48] However, Dr Vieta observed that, in many cases, existing antidepressant treatment is maintained during manic episodes. The most powerful reason for this practice was found to be the presence of depressive symptoms during mania.[49] Other reasons included rapid cycling, a high number of previous depressive episodes, and anxiety at baseline. In Dr Vieta's view, when clinicians observe predictors of depression, they try to address the risk with antidepressants, although guidelines and evidence do not support antidepressant use in these instances.

Benefits and Risks of Long-Term Antidepressant Use

Dr Vieta commented that, in clinical practice, if a patient responds to an antidepressant in the acute phase of treatment for a depressive episode, antidepressants are likely to be used during the maintenance phase. A meta-analysis[50] of long-term studies, however, reported that, compared with mood stabilizer treatment alone, adjunctive antidepressant use provided little depression prophylaxis, and a trend (although not significant) toward increased mania was found (Table 2).[51–57]

In contrast, a 1-year follow-up study[58] of patients who had achieved remission from a bipolar depressive episode with the addition of an antidepressant to an ongoing mood stabilizer (about 15% of the study cohort) reported that 36% of those who continued the antidepressant had a depressive relapse versus 70% of those who discontinued the antidepressant. Dr Vieta observed that these data are consistent with his clinical experience, that in those patients for whom antidepressants *are* effective, continuing the antidepressant is reasonable.

A study[59] suggests that the combination of olanzapine and fluoxetine may be useful in long-term treatment. Patients who responded to the combination in acute phase treatment received either continued treatment with the combination or olanzapine alone for 12 weeks. More patients receiving the combination (71%) maintained remission than those switched to olanzapine monotherapy (40%). In addition, when the olanzapine/fluoxetine combination and lamotrigine monotherapy were compared over 25 weeks,[60] the combination treatment produced greater symptom improvement. However, patients taking olanzapine/fluoxetine had more side effects, in particular metabolic issues and weight gain, compared with those taking lamotrigine. No differences were found in the incidence of relapse or manic switch.

The Polarity Index

Dr Vieta explained that both acute and long-term treatment of bipolar disorder should be influenced by the predominant polarity of the patient. Depressive episodes can be exactly the same in both polarities, but an antidepressant would be a poor choice in a depressed patient prone to mania, because it would likely cause a switch to mania or at least fail to prevent it. In a patient prone to depression, lamotrigine might be ideal treatment, but an antidepressant might also be appropriate.

Dr Vieta then discussed the polarity index,[61] which was developed to better understand how drugs compare in preventing manic and depressive episodes. The polarity index is a metric based on number-needed-to-treat (NNT) values for mania and depression from placebo-controlled, long-term studies; by calculating the NNT for each polarity, a metric can be created that quantifies if a drug is better at preventing mania than preventing depression.[62] A polarity index greater than 1 means that the drug prevents mania better than depression, while numbers less than 1 indicate better efficacy for depression.

Conclusion

Dr Vieta concluded that the evidence base for the use of antidepressants in bipolar depression is poor but suggests that antidepressants should not be used as monotherapy.

Adjunctive antidepressants may be used in bipolar disorder when first-line treatment fails, but should not be used in patients with a history of mixed episodes or rapid cycling.

Among antidepressants, fluoxetine has the best evidence base, but patients taking SNRIs or TCAs should be monitored for manic switch. Antidepressants may be used adjunctively over the long-term in patients who have responded to antidepressants as acute treatment after failure of first-line treatment or in patients with comorbidities such as obsessive-compulsive disorder and other anxiety disorders. Further research is needed to qualify issues like switch risk and cycle acceleration.

INTERNATIONAL GUIDELINES

Shigenobu Kanba, MD, PhD; Kyooseob Ha, MD, PhD; Ayşegül Özerdem, MD, PhD; and Gustavo H. Vázquez, MD, PhD, next presented information regarding maintenance treatment guidelines for bipolar depression and standards of care in their respective countries (Table 3).[63–66] Each faculty member stressed that successful maintenance treatment of bipolar disorder is based on many factors, including an early and correct diagnosis and appropriate acute care of depressive episodes.

Japan

Dr Kanba stated that many drugs are approved in Japan to treat manic episodes, but, at this time, none are approved for bipolar depression or maintenance treatment. Olanzapine recently became the first atypical antipsychotic agent to be approved in Japan for treating bipolar mania, and lamotrigine is expected to be approved for maintenance use in bipolar disorder in 2011. However, psychiatrists in Japan can choose to follow international treatment guidelines and use available medications off-label.

Dr Kanba related that the Japanese Society of Mood Disorders, using data from Japan and from randomized controlled studies or meta-analyses from other areas of the world, has recently published a treatment guideline[63] for bipolar disorders. The most highly recommended therapy for acute bipolar depression in the guideline is monotherapy with quetiapine or lithium; the second-level recommendation is monotherapy with olanzapine or lamotrigine. If combination therapy is needed for bipolar depression, lithium plus lamotrigine is recommended. Electroconvulsive therapy (ECT) is also an option. The guideline does not recommend antidepressants for bipolar depression, but does recommend the concomitant use of interventions such as psychoeducation and cognitive and interpersonal therapies. Maintenance therapy is detailed in Table 3.

Korea

Dr Ha informed the group that Korea has a lower reported incidence of bipolar disorder than that seen in Western countries and that the lower prevalence may be due partly to misdiagnosis and underdiagnosis.[67,68] For example, hospitals have reported a high ratio of manic to depressed bipolar patients, which may mean that patients with bipolar depression may be diagnosed with unipolar depression.[69] Unipolar depression is more culturally acceptable, and psychiatrists may be reluctant to make a bipolar disorder diagnosis because of stigma unless they confirm a definite manic episode. A 2009 study[70]

Table 3. Maintenance Treatment Guidelines for Bipolar Depression by Country[a]

Japan: Japanese Society of Mood Disorders, 2011	Korea: Korean Medication Algorithm for Bipolar Disorder, 2006	Turkey: Psychiatric Association of Turkey, 2010	Argentina, 2010
No guideline is provided for maintenance treatment of bipolar depression. Guidelines for maintenance treatment of bipolar disorder are as follows: Most recommended: LI Next recommended: OLZ, LTG, QUE (as an adjunct to LI or VPA), LI + LTG, LI + VPA, ARI, VPA Other recommended treatments: CBZ, RIS depot (for poor adherence despite extensive psychoeducation), other combinations of MSs, MS + AAP, thyroid hormone	Bipolar I: First-line: No preferred treatment Second-line: MS + AAP, MS alone, MS + LTG Low second-line: 2 MS, AAP + LTG, LTG alone Bipolar II: First-line: No preferred treatment Second-line: MS + LTG, MS alone (VPA, LI, LTG), MS + AAP, MS + AD Low second-line: AAP + LTG, LTG alone, AAP alone Psychosocial approaches should also be used	Continue successful mood stabilizer and/or atypical antipsychotic from the acute episode (LI, VPA, CBZ, QUE) Taper off antidepressants, if used. A small group of patients, usually with bipolar II disorder, may need to take antidepressants longer. If patients continue antidepressants, use adjunctive mood stabilizers LTG can be used as monotherapy for those with Bipolar II or rapid cycling, and as an adjunct to prevent depressive relapses	Bipolar I disorder, depressive predominance: LI + LTG Bipolar I disorder, manic predominance: LI + VAL For rapid cycling, LI + OLZ, ARI, or QUE In resistant cases, 3 MSs + QUE/OLZ can be combined, or use ECT Bipolar II disorder: LTG or LI or LTG + LI For rapid cycling, add QUE An antidepressant or atypical antipsychotic or other augmentation can be added if needed, or ECT can be used

[a]Based on Kato et al,[63] Yoon et al,[64] Aydemir et al,[65] and Streijilevich et al.[66]

Abbreviations: AAP = atypical antipsychotic, AD = antidepressant, ARI = aripiprazole, CBZ = carbamazepine, ECT = electroconvulsive therapy, LI = lithium, LTG = lamotrigine, MS = mood stabilizer, OLZ = olanzapine, QUE = quetiapine, RIS = risperidone, VAL = valproate, VPA = valproic acid.

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showed that patients with an initial episode of depression were subject to much greater delays in receiving a diagnosis of bipolar disorder than patients with initial manic episodes (5.6 years versus 2.5 years, respectively). Because of this misdiagnosis, patients with bipolar disorder often receive antidepressant monotherapy.

Dr Ha observed that clinicians in Korea have traditionally believed that mood stabilizers are antimanic agents, with no antidepressive properties, while antidepressants are considered effective for depression, whether unipolar or bipolar. Because they believe that mood stabilizers and atypical antipsychotics can *cause* depression, clinicians reduce dosages of those drugs as soon as a patient improves and add an antidepressant or lamotrigine if the patient becomes depressed, then discontinue the antidepressant and increase the dose of the mood stabilizers and/or antipsychotic when the patient has another manic or hypomanic episode. These practices create a treatment cycle that follows the symptom changes of the patient rather than a treatment regimen that prevents episodes.

Surveys of clinicians[64,71,72] have shown that treatment strategies are evolving in Korea, moving away from mood stabilizers and toward atypical antipsychotics for managing manic episodes. Expert consensus guidelines[73] have been revised[64,71] in the past decade, and the revisions reflect an increasing preference for atypical antipsychotics and lamotrigine and a declining preference for carbamazepine, typical antipsychotics, and antidepressants in the treatment of bipolar disorder. Quetiapine is the only drug approved in Korea to treat acute bipolar depression. For drugs recommended for maintenance treatment, see Table 3.

Dr Ha concluded by saying that psychoeducation is encouraged to help the patient accept their diagnosis, maintain a healthy lifestyle, and adhere to their treatment. Patients should also be taught how to use a mood chart so that they and their families can recognize early signs of relapse.

Turkey

Dr Özerdem stated that the treatment guideline[65] for bipolar disorder published by the Psychiatric Association of Turkey in 2010 is evidence- and consensus-based. The chapter[74] on the treatment of acute bipolar depressive episodes recommends different strategies depending on severity (ie, mild to moderate, severe nonpsychotic, or severe psychotic). Lithium, valproate, and carbamazepine are the first-line mood stabilizers recommended for bipolar depression, either alone or with adjunctive medications chosen according to the severity of the episode, with additional steps available for nonresponse or partial response. Antidepressants, other than those affecting multiple neurotransmitter systems such as TCAs and SNRIs, are an option from the first stage of treatment on, but only as adjuncts to a mood stabilizer and/or an atypical antipsychotic; for severe depression, TCAs are allowed if the first-line treatment produced an insufficient response. Quetiapine is approved as a treatment for acute bipolar depression in Turkey, but the algorithm recommends that it be used as an adjunctive medication with a mood stabilizer. If earlier treatments have failed, new combinations (such as adding lamotrigine, especially in severe depression) or ECT or transcranial magnetic stimulation (TMS) can be tried. ECT is recommended at early stages of treatment only in severe cases.

The guidelines recommend tapering and discontinuing antidepressants soon after remission of the depressive episode (preferably sometime between 2 to 6 months) due to the risk of manic switching. Dr Özerdem pointed out that about 20% of patients, mostly those with bipolar II disorder, will need to continue taking antidepressants for longer periods (see Table 3).

For the prevention of depression, the treatment guidelines[75] recommend lithium for its antidepressant efficacy and its antisuicidal effect.[76] Lamotrigine can be used as monotherapy for bipolar II disorder and in patients with rapid cycling, who have a greater risk of manic switching with antidepressants; lamotrigine is also recommended as an adjunct in other patients if depressive relapses cannot be prevented otherwise. Valproate and carbamazepine are recommended in maintenance treatment for preventing manic switches for patients who are taking antidepressants. Quetiapine is recommended as monotherapy for maintenance treatment, and olanzapine may be effective in preventing depression. Aripiprazole is not recommended for prevention of depression. The other atypical antipsychotics are not mentioned in the guidelines for prevention of depression.

Dr Özerdem concluded by saying that guidelines for the treatment and prevention of bipolar disorder are useful tools for clinicians, but, despite extensive specialized care and aggressive treatment, a certain percentage of patients will continue to suffer from either clinical or subclinical depression. The reasons behind patients not achieving euthymia may not be directly related to comorbid conditions but may be associated with underlying pathogenesis. In particular, she recommended that special attention should be paid to female patients and to fluctuations in thyroid function. Misdiagnosis in patients with bipolar II disorder may also be high, causing delay in appropriate treatment and a more complicated course of illness.

Argentina

Dr Vázquez summarized the Argentine Association of Biological Psychiatry guidelines for treating acute bipolar depression, which were based on a combination of data gained from evidence-based pharmacotherapy trials and the clinical experience of experts in psychiatry. The original guideline, published in 2005,[77] recommended monotherapy for maintenance treatment mainly because most drugs were not approved for maintenance treatment at that time. The maintenance section of the treatment guideline was updated in 2010[66] to incorporate the clinical aspect of predominant polarity (see Table 3). For patients with bipolar I disorder, the guidelines recommend beginning patients with lithium, then, if the patient has predominant mania, add valproate;

for a patient with predominant depression, the guidelines recommend adding lamotrigine. For patients with rapid-cycling bipolar I disorder, the guidelines recommend adding an atypical antipsychotic (ie, quetiapine, olanzapine, or aripiprazole for predominant mania or quetiapine for predominant depression).

For bipolar II disorder, Dr Vázquez pointed out that the guidelines stressed that clinicians should first examine the history of the patient to search for signs of rapid cycling so that antidepressants can be avoided. If the patient has rapid cycling, combination therapy with lamotrigine, lithium, and quetiapine is the first step. If there is no sign of rapid cycling, the guidelines recommend using either lamotrigine or lithium; the next step is to use lithium and lamotrigine in combination. Antidepressants are generally avoided in maintenance treatment but may be added for patients without rapid cycling. Further resistance can be treated with an atypical antipsychotic, including clozapine, or ECT.

Dr Vázquez concluded by stressing the importance of differentiating between unipolar and bipolar depression to avoid using inappropriate medications in patients with bipolar disorder, particularly unopposed antidepressants because of the potential risk of inducing manic switching or rapid cycling. Dr Vázquez explained that the guidelines recommend that, if antidepressants are used, they should be prescribed for up to 8 weeks after remission and then discontinued slowly. When planning treatment for patients with bipolar I disorder, their predominant polarity should be considered. A history of rapid cycling should also be a factor in maintenance treatment decisions.

INTERNATIONAL CONSENSUS GROUP ON DEPRESSION IN BIPOLAR DISORDER

After the group reviewed the evidence base and heard presentations on international guidelines, Dr Frye led a discussion to reach consensus on what an international standard of care would include (Table 4). Highlights of that conversation follow.

Dr Frye: Our purpose today has been to conceptualize the evidence-based literature regarding depression prophylaxis in the treatment of bipolar disorder to reach a consensus on treatment guidelines. To that end, we have heard presentations from an international faculty on a variety of topics, including the evidence base for maintenance pharmacotherapy and the clinical translation of that evidence, which includes monitoring for side effects from approved medications. We have also reviewed acute management prerequisites and bipolar depression prevention and treatment guidelines from around the world. Let us begin with how trial design affects the evidence base.

Evidence Base: Trial Design

Dr Frye: One key change in trial design over the last 10 to 15 years has been a greater focus on stabilization criteria and enrichment. In the studies reviewed, the length of the stabilization period correlated to the length of the time-to-relapse outcome measure in the randomization phase. Patients who were stabilized for 2 weeks before randomization relapsed in a shorter period of time than patients who were stabilized for 4 weeks, and even more so in comparison with patients who were stabilized for 6 weeks.

Table 4. International Consensus for the Treatment and Prevention of Bipolar Depression

Trial Design Consensus
Stage I: Screening Stage
I. Accept patients with either bipolar I or bipolar II disorder who are either currently or recently manic or depressed
II. Determine patient's pole predominance
III. Patients are enriched for the study medication
Stage II: Stabilization Phase
I. 8 to 12 weeks minimum range for stabilization
Stage III: Randomization Phase
I. Trials should last 6 months
II. Enrichment drug should be withdrawn over 1 to 2 weeks
III. Trials should be powered to separate for mania and depression episodes
Maintenance Treatment Consensus for Depression Prophylaxis
I. Continue acute medication. First-line acute recommendations for bipolar depression are quetiapine, lithium, and lamotrigine
II. Consider patient medical comorbidities and medication adverse event profiles when choosing treatments
III. Initiate preventive measures, including diet and exercise, if medications with metabolic effects (including weight gain, dyslipidemia, and prolactin effects) are chosen. Monitor thyroid levels, especially for patients taking lithium
IV. Antidepressant monotherapy is not recommended
V. Patients who responded to antidepressants as a second- or third-line treatment in the acute phase can be maintained on antidepressant treatment in combination with a mood stabilizer, except in the patients with rapid cycling or mixed episodes
Depression Prophylaxis
I. Continue successful medication from the acute phase. Quetiapine, lithium, and lamotrigine are recommendations for a depressive acute episode
II. Taper antidepressants in the maintenance phase (if used), unless the patient has a history of relapse after discontinuing antidepressants
III. Lithium is recommended as the first line (and for those with suicidal ideation or previous suicide attempts), but should be administered at an adequate dosage for an adequate duration
IV. Lamotrigine is preferred for patients with a predominance of depression, atypical depression, or obesity or medical comorbidities. Lamotrigine is not recommended for patients with mixed episodes. Lamotrigine is not appropriate as monotherapy for depression with psychotic features, but can be combined with an antipsychotic. Lamotrigine is recommended for patients with a history of switching while on antidepressant treatment.
V. Olanzapine or quetiapine is preferred for patients with a predominance of mania and without obesity or diabetes mellitus, and who do not gain weight while taking the drug
VI. Quetiapine plus lamotrigine, lamotrigine plus lithium, lithium plus quetiapine, or all 3 medications can be used in combination
VII. Long-acting risperidone is appropriate for patients with adherence issues, but patients should be monitored for prolactin side effects
VIII. Valproate may be effective for maintenance treatment of bipolar disorder
IX. Maintenance ECT may be recommended for treatment-resistant patients
X. Patient and family psychoeducation are encouraged

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Enrichment refers to a trial design in which patients who have responded to the medication in the stabilization phase then go on to test long-term prophylaxis. Enrichment trials resemble clinical practice and help to answer the question as to whether a patient should be continued on a medicine after stabilization. But clearly, the value of enrichment should not be gained at the expense of generalizability.

Dr Vieta: Another critical issue in trial design is the index episode of the patients. Most of the studies that have positive data for medications preventing depression are the ones that enrolled patients during the depressive phase.[4,7]

Dr Özerdem: The duration of the follow-up period should also be considered—that is, whether a follow-up period of 6 weeks, 8 weeks, or 6 months, as opposed to 2 years, makes any difference in terms of the efficacy of maintenance treatment.

Dr Frye: Looking at dropouts and cost concerns, a 6-month randomized phase seems best.

Dr Vieta: If time to relapse is the primary outcome, the study does not need to last longer than 6 months because most relapse events happen early. Of course, in terms of safety and tolerability, it would be very interesting to see longer data—2 years, for instance.

Dr Özerdem: It is important to state that a 6-month time frame is sufficient, because many clinicians say they do not trust the data in maintenance studies because they are limited to a certain period of time.

Dr Vieta: Six months is sufficient, particularly because a clinical trial is an experiment that exposes patients to placebo. As patients go untreated for the period of time of the trial, studies should not go on any longer than necessary.

Dr Vázquez: On the other hand, what about studies that show that patients without rapid cycling have a cycle of around 12 or 13 months as part of the natural process of the illness?[78] If we just follow them for a 6-month period, we could lose part of a natural cycle.

Dr Vieta: The trial is designed to detect the first episode that occurs in patients who relapse. From a naturalistic point of view, we would follow the patients even after they relapse. But, for a clinical trial, and especially a placebo-controlled trial, the goal is to prove that the patients take longer to relapse in one arm of the trial than in the other.

Dr Frye: From a consensus standpoint, do we agree on the standard clinical trial design? Regulatory trial designs have efficacy as their primary outcome measure, but studies should be designed to both minimize placebo exposure and be cost-conscious. Also, so that the trial has as much generalizability as possible, the screening phase, or Stage I, of the trial should accept patients with either bipolar I or bipolar II disorder who are either currently or recently manic or depressed.

Dr Kanba: We have fewer data for bipolar II disorder patients. We need to make sure patients with bipolar II disorder are included so that we can pull out the data for this group of patients.

Dr Frye: Next, Stage II of a clinical trial is stabilization, and 8 weeks is viewed as a minimum duration; probably 8 to 12 weeks should be the minimum range for stabilization. Finally, we propose that the randomization phase, or Stage III, should last 6 months.

Dr Kato: We cannot discriminate real preventive effect from withdrawal effect in the protocol enrichment. Patients can experience discontinuation symptoms with lithium and antipsychotics if you stop them quickly.

Dr Vázquez: A recently published study[79] states that patients also have an increased risk of early illness recurrence after rapid discontinuation of antidepressants.

Dr Frye: So what would be a reasonable time period for withdrawal of the medication? Treatment recommendations need to be simple. I try to taper a medicine over the course of a week or try a 50% reduction for a couple of days and then another 50% reduction for a couple of days.

Dr Vieta: I would recommend 2 weeks in a trial. One to 2 weeks is a good compromise, depending on the compound.

Dr Frye: Then we agree that, between 1 and 2 weeks after randomization, the study participants are definitely off the stabilization medicine and fully on placebo.

Dr Kanba: In clinical practice, discontinuation takes longer.

Dr Kato: Bipolar disorder should be treated for decades, but the longest period for clinical trials is 2 years. Therefore, we should also learn from epidemiologic studies.

Dr Frye: Two years of follow-up is the minimum needed for some medical comorbidity concerns. Knowing the long-term adverse effect profile of these medications is critical, but we may get meaningful data in a naturalistic study that would not have the placebo exposure or regulatory monitoring.

Dr Vieta: In the naturalistic EMBLEM study,[80] 54% of the patients had changed medication in the first 3 months. So, it is difficult to calculate, from the safety perspective, which long-term side effect is related to which medication. Naturalistic data are relevant for practice but scientifically difficult.

Dr Frye: And, finally, the studies should ideally be powered to separate findings for mania and depression. Therefore, individual patient polarity should be considered in trial design, because, as Dr Vieta showed, one factor that affects how the evidence base is translated into clinical practice is the predominant polarity of the patient.

Acute and Maintenance Treatment of Bipolar Depression

Dr Frye: The importance of making the correct diagnosis of bipolar disorder was highlighted in today's presentations, and it is the first step in acute care. Bipolar disorder is often misdiagnosed as unipolar depression, which can delay appropriate treatment for years and expose the patient to treatment that may be harmful. We discussed the patient's predominant polarity as a factor in trial design. How does that translate into clinical recommendations?

Dr Vázquez: Patients with bipolar I disorder, on the whole, have a more balanced number of episodes, and those with bipolar II have more depressive episodes. One study[81] determined predominant polarity based on a 2:1 or greater ratio

of previous episodes of mania-hypomania to depression, and nearly half had a predominant polarity.

Dr Frye: So the patient may have either a depressive- or manic-predominant polarity. There is also a polarity index for medications, based on the number-needed-to-treat for depression or mania.[62] On Dr Vieta's scale, the drugs effective for depression prophylaxis had an index below 1.0.

Dr Vieta: Yes, you determine the pole predominance of the patient and the polarity index for the treatments and try to correlate the two. The only compounds that have a polarity index for depression prophylaxis below 1.0 are lamotrigine and quetiapine.

Dr Frye: Are we in agreement that the first-line treatment recommendations for a depressive-predominant patient are quetiapine and lamotrigine? Is there another medication you would recommend?

Dr Kanba: I want to add lithium, even though its polarity index is over 1.

Dr Vieta: Yes—we did not discuss one trial[82] of quetiapine monotherapy for maintenance treatment that is also relevant in regard to lithium. Patients were stabilized with quetiapine and then were randomly assigned to receive placebo, quetiapine monotherapy, or lithium monotherapy. Because the sample was not enriched for lithium, the trial acted as a prophylactic study of lithium. Lithium and quetiapine both separated from placebo in preventing any mood episode, and the results suggest that you can treat mania or depression with one compound—say, quetiapine—and still maintain prophylaxis if you switch to lithium.

Dr Özerdem: Olanzapine plus fluoxetine appears to be as effective as lamotrigine in relapse prevention in bipolar I depression maintenance treatment.[60]

Adverse Effects and Medical Comorbidities

Dr Frye: Are there medical comorbidities or adverse event profiles that lead you to use one medicine or another? Weight—either in the sense that someone is obese to begin with or current concerns of weight gain—seems to be a strong deciding factor.

Dr Özerdem: When we discussed weight gain, we focused more on preventing weight gain with medication or overcoming weight gain problems with medication. However, I do think that, beyond medications, we need to care about physical exercise and a change in lifestyle, because that is also crucial for the treatment and prevention of depression.

Dr Frye: Atypical symptoms of depression—hypersomnia, hyperphagia, psychomotor retardation—beget weight gain, so a multifaceted approach to treating depression is needed. That being said, there is a patient subgroup that, whether simply by their illness presentation or by their choice, asks about weight neutrality from the very beginning, and patient preference should be considered.

Dr Vieta: In maintenance treatment, side effects related to prolactin, such as sexual dysfunction and amenorrhea, are also relevant.

Dr Vázquez: Elevated prolactin levels have been demonstrated to cause osteoporosis in the long term.[83]

Dr Frye: If the upper limit of a normal TSH level is lowered to follow the new guidelines that Dr McElroy mentioned, more psychiatrists will be looking at thyroid hormone augmentation. Thyroid augmentation can also contribute to osteopenia or osteoporosis,[84] so thyroid levels should be monitored.

Dr Vieta: My concern is that patients with bipolar II disorder, because they have a greater burden of depression and a lesser burden of mania, might be more sensitive to long-term neurologic side effects such as tardive dyskinesia or extrapyramidal symptoms (EPS).

Role of Antidepressants

Dr Frye: What lessons do we take from the antidepressant evidence base in the acute treatment of bipolar disorder?

Dr Vieta: Antidepressants should not be a first-line treatment. But, there are patients who need second- or third-line treatments, and it makes sense to try antidepressants. For those who respond to antidepressants as a second- or third-line treatment, the data are more supportive of staying on the antidepressant rather than stopping it.

Dr Ha: I agree, in combination with mood stabilizers.

Dr Frye: Clearly, antidepressant monotherapy is not a treatment for bipolar depression, either acutely or for maintenance.

Dr Vázquez: Yes, but in clinical practice, if in the acute phase you have successfully treated your patient with bipolar depression, and that patient is stable, you could maintain the adjunctive antidepressant treatment and not interrupt it abruptly. We must make our colleagues aware that removing antidepressants could also cause a patient to relapse on depression. We also have to think about avoiding antidepressant prescription for rapid-cycling patients.

Dr Vieta: Yes, the advice would be to keep the adjunctive antidepressant in those who have responded and who have no rapid cycling and no mixed episodes.

Dr Frye: So, no first-line antidepressant monotherapy for bipolar depression. What about well-intentioned clinicians trying to treat symptoms of depression or anxiety? What message do we give those clinicians about using strategies that seem to be at odds with the evidence base on antidepressants in bipolar disorder?

Dr Vázquez: That antidepressants could be effective for some patients, but not for all. We have to divide our patients clinically, because it is not a question of using or not using antidepressants, but a question of in which patients are you going to use antidepressants.

Dr Özerdem: When we say that antidepressants are not recommended as first-line, are we considering the most severe cases, where you have to choose between ECT or any other choice?

Dr Vázquez: We put antidepressants first-line in the Latin American guidelines for severe bipolar depression.

Dr Özerdem: As an adjunct to mood stabilizers.

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Dr Vieta: But why would you not try quetiapine, for instance?

Dr Özerdem: We also have that option.

Dr Frye: Are you starting them simultaneously, in an accelerating or cotherapy design?

Dr Özerdem: Yes, for patients with severe illness.

Dr Frye: If someone is profoundly depressed, are you going to start them on lithium, quetiapine, and an antidepressant simultaneously?

Dr Özerdem: Yes, in the most severe cases. In cases that are still severe but not the most severe, it could be a mood stabilizer plus antidepressant.

Dr Frye: So, we agree that antidepressant monotherapy is not first-line, but, in severe cases—except in the case of patients with rapid cycling—an antidepressant may be used in conjunction with mood stabilizers. Are there any other recommendations for the role of antidepressants in the maintenance phase?

Dr Vázquez: How long should antidepressants be used?

Dr Vieta: Maintain antidepressants until the patient worsens again, because if the patient is well you maintain the regimen that made him or her well.

Dr Frye: Are we obliged to taper the patient off the antidepressant at least once to determine if it is still needed?

Dr Vázquez: Most of our patients do that on their own, when they feel better.

Dr Vieta: In my opinion, if the patient is doing well on a medication, they should stay on it, because bipolar disorder is such a terrible illness. We do not need to experiment when something is working and tolerable.

Dr Özerdem: It is crucial to look at a patient's history. If the patient has stopped taking the antidepressant by himself or herself and then relapsed into depression, that is a predictor that the antidepressant should be continued. So, we may not want to discontinue antidepressants experimentally on our own, but we should look at the patient's history of relapse following antidepressant discontinuation.

Treatment-Resistant Depression

Dr Frye: The criteria for treatment-resistant unipolar depression generally focus on the number of medications that have failed in the patient's treatment regimen.[85] However, we have discussed the possibility of a primary thyroid pathology or a noradrenergic underlying neurobiology that could be affiliated with treatment resistance in bipolar disorder. Are there other neurobiological variables that could be associated with treatment resistance?

Dr Özerdem: What about the delay in initiating bipolar treatment due to misdiagnosis as a factor in treatment-resistance? I am referring to patients who appear to have recurrent unipolar depression until they convert into bipolar disorder, either by switching on antidepressants or by spontaneously switching, so they have been prescribed antidepressants in the past.

Dr Frye: Misdiagnosis can cause patients to receive either no treatment or incorrect treatment and that could be a factor contributing to the virulence of the treatment resistance, as opposed to pharmacotherapy failure.

We have had information presented that antidepressant use in bipolar disorder is associated with higher switch rates, more mixed episodes, and more suicide attempts. There might be something about the disease phenomenology that makes some treatments contribute to the degree of treatment resistance.

Recommendations for Depression Prophylaxis

Dr Frye: Now, given the evidence base, the adverse event profiles, what we know about the illness over time, and the local input that we have had today, what recommendations can we give for depression prophylaxis in bipolar disorder? What are the roles of lamotrigine and quetiapine?

Dr Ha: We do not have head-to-head results between the 2 compounds.

Dr Frye: How do you choose which one of these drugs to use for maintenance treatment, outside of strict regulatory authority?

Dr Ha: If I start quetiapine or other atypical antipsychotics during the manic phase and the patient becomes depressed, I continue quetiapine. If a patient starts lamotrigine during the depressed phase and gets better, I keep him or her on lamotrigine.

Dr Frye: So part of the recommendation for depression prophylaxis relates to what has been successful in the acute phase. The acute phase treatment is relevant here, and, if an antidepressant was used, we would try to take the patient off the antidepressant, unless there is a clear history that the patient relapses after discontinuing antidepressants.

Is there a certain patient you think of with regard to lamotrigine versus quetiapine or other antipsychotics?

Dr Vieta: My rule is that lamotrigine is better for patients with a predominance of depression and with an absence of psychotic features, unless you combine it with an antipsychotic. I prefer lamotrigine for those who have a predominance of depression but not for those who have a predominance of mania. I also prefer it for patients who have obesity and medical comorbidities, as opposed to quetiapine, which is a compound that has some liability for obesity and comorbidities. I also look at features of the depression. In patients who have atypical symptoms, I think lamotrigine is the better choice. I would use quetiapine instead of lamotrigine in patients with mixed episodes.

Dr Ha: From my clinical experience, for those who have more chronic depressive symptoms, I prefer lamotrigine.

Dr Frye: So, lamotrigine is preferred for depressive-predominant bipolar disease when weight neutrality and metabolics are a concern. However, we can recommend avoiding lamotrigine maintenance prophylaxis when there has been a mixed presentation.

Dr Vieta: Yes, and lamotrigine is not appropriate as monotherapy for depression with psychotic features, but can be combined with an antipsychotic.

Dr Vázquez: What about treating patients with anxiety comorbidity?

Dr Vieta: Quetiapine has good data in anxious patients, as well as olanzapine and divalproex.[86]

Dr Frye: Is there a pattern of patients that you think of for quetiapine maintenance monotherapy?

Dr Kato: The data for quetiapine monotherapy for maintenance have not yet been published.

Dr Özerdem: Patients with a history of mood switching with antidepressants are good candidates for lamotrigine maintenance therapy.

Dr Frye: The one caveat I would have is that I get uncomfortable using a lamotrigine-antidepressant combination in someone who might have manic-predominant disease. We know from the evidence base[4] that lamotrigine is better than placebo in time-to-intervention for mania, but when you add an antidepressant, the risk of mood switching is greater.

Let's discuss quetiapine monotherapy, which we have already mentioned in relation to mixed presentations.

Dr Ha: Quetiapine would be useful for depression with psychotic symptoms.

Dr Frye: Are there any other patients for whom we would think about quetiapine maintenance?

Dr Vázquez: Patients with bipolar I disorder for antimanic prevention.

Dr Frye: What type of patient is lithium maintenance appropriate for, other than acute responders? Lithium is not an easy drug to work with in the maintenance phase.

Dr Özerdem: Right. These patients usually have the more classic type of bipolar disorder, without many complications, and good treatment compliance.

Dr Vázquez: Perhaps that situation is due to how we manage our patients. Perhaps these patients would be responders on other drugs also, but we start them on lithium. And the patients who are taking 2 or 3 drugs are not good responders, so we add another mood stabilizer and then another.

Dr Frye: In my clinic, the robust lithium responders are all 60 years old or older and have been on the medication for decades. The profile of a typical lithium responder is a geriatric patient who began treatment with lithium when he or she was 30 years old and has been on a single medicine for his or her entire life.

Dr Özerdem: Is it possible that the next generation has not been given the chance for lithium?

Dr Frye: You could argue that we clinicians went right to antipsychotics and anticonvulsants for ease of use.

Dr Vázquez: And there is also a physician age factor, because in Latin America, you can see that physicians who are 50 years old or older usually prescribe lithium. Moreover, it is not only a question of age but of expertise.

Dr Ha: Adequate dosage and duration is key to bipolar depression treatment with most medications, because most medications are more effective for mania than depression. Most failures come from using an inadequate dosage of medication for a short duration clinically.

Dr Frye: Does anyone have any comments in reference to other medications? For instance, with the long-acting injectable risperidone, there is a positive aspect in terms of adherence versus the negative aspect of prolactin-related side effects. Does anything come to mind with ziprasidone, olanzapine, and aripiprazole? To me, this is a weight-neutrality issue.

Dr Vieta: But aripiprazole is not weight-neutral. Ziprasidone is. Aripiprazole is not free of weight gain, but it looks better because most of the patients are switched from olanzapine and then they lose weight. But, in my experience, at least 20% of the patients have clinically significant weight gain with aripiprazole. And if you look at the Keck et al study,[87] 20% of the patients taking aripiprazole had a clinically significant weight increase after 2 years, which fits my clinical experience.

Dr Özerdem: And there are also EPS with aripiprazole.

Dr Frye: What type of patient needs olanzapine maintenance therapy? I have one patient who is now taking lithium, valproate, and olanzapine, and olanzapine is the only antipsychotic that has gotten him out of mania. He is a very refractory patient who has had relapses with drug discontinuation.

Dr Vieta: Olanzapine is a good drug except for the weight-gain issue.

Dr Ha: Actually, some patient groups do not gain weight, even with olanzapine.

Dr Frye: We did not talk much about carbamazepine. There is a mindset, at least with residents at my clinic, that even when they have made the conscientious decision to select carbamazepine, they do not. They choose oxcarbazepine, thinking that it is easier to use and has a better evidence base.

Dr Vieta: Valproate has been found effective for both acute[88] and maintenance[89] treatment of bipolar depression. I think we should mention maintenance ECT, even though there are few data in the evidence base. We use ECT in my clinic, and it works very well.

Dr Özerdem: Yes, absolutely. We do ECT as well, and it is the only thing that works in some patients.

Dr Frye: Other recommendations, besides ECT, have a small evidence base. Clozapine has shown very mild antidepressant response but improvement of mania.[90] What about psychotherapy?

Dr Vieta: Effective prevention of any mood episode has been shown with adjunctive cognitive-behavioral therapy and psychoeducation in patients who are in remission.[91,92]

Dr Vázquez: Does psychoeducation work better for mania than for depression?

Dr Vieta: Patient group psychoeducation seems to work to prevent both, but family psychoeducation was only better at preventing mania.[93]

Dr Ha: Lifestyle modification should be added as well.

Conclusion

Dr Frye: Are there any closing thoughts?

Dr Kato: Antidepressants are still some of the most frequently prescribed drugs for bipolar depression. None of us

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have suggested that antidepressants are first-choice drugs for bipolar disorder, so we should determine why they are still used so often and what we can do to rectify the situation.

Dr Frye: There is a real disconnect.

Dr Kato: Yes, and we discussed several possible explanations. For example, the age of the physicians may affect the clinic's prescriptions, or patients may demand antidepressants.

Dr Vázquez: True. Once a patient experiences a hypomanic state due to an antidepressant, they may keep asking for the antidepressant.

Dr Kato: Yes, and to manage this situation, education for patients—and for physicians—is needed.

Dr Özerdem: I have observed that clinicians, especially young clinicians, tend to change medications very quickly. For instance, if the patient is having depressive symptomatology for a week or so, young clinicians immediately ask whether they should initiate lamotrigine or antidepressants. We try to teach them to slow down. Does this happen everywhere, and does it also happen in the maintenance phase? Perhaps we move too quickly because we are afraid of bipolar illness—because when the patients get ill, they get really ill—and we want to prevent it.

Dr Vázquez: That is also true in my country.

Dr Kato: Physicians may also tend to prescribe antidepressants because of their own feelings of helplessness.

Dr Frye: I think a lot of these interventions are well-intentioned. Clinicians are recognizing the patient's predominant polarity of depression, with or without anxiety, and trying to treat that as best as they can. This problem really highlights how little we know about the most effective strategies to treat and prevent bipolar depression. However, consensus guidelines derived from the pharmacotherapy evidence base and international standards of care can help to improve outcomes when managing patients with this serious and debilitating illness.

Drug names: aripiprazole (Abilify), bupropion (Aplenzin, Wellbutrin, and others), carbamazepine (Carbatrol, Equetro, and others), clozapine (Clozaril, FazaClo, and others), divalproex (Depakote and others), fluoxetine (Prozac and others), imipramine (Tofranil and others), lamotrigine (Lamictal), lithium (Lithobid and others), metformin (Flucophage, Glumetza, and others), olanzapine (Zyprexa), olanzapine/fluoxetine combination (Symbyax), oxcarbazepine (Tripletail and others), paroxetine (Paxil, Pexeva, and others), quetiapine (Seroquel), risperidone (Risperdal and others), sertraline (Zoloft and others), valproic acid (Depakene, Stavzor, and others), venlafaxine (Effexor and others), ziprasidone (Geodon).

Disclosure of off-label usage: The chair has determined that, to the best of his knowledge, amitriptyline, bupropion, fluoxetine, imipramine, paroxetine, sertraline, and venlafaxine are not approved by the US Food and Drug Administration for the treatment of bipolar depression.

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For the CME Posttest for this article, see pages 1311–1312.