Selecting Appropriate Treatments for Maintenance Therapy for Bipolar Disorder

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Long-term management of bipolar disorder is a crucial component of treatment because the recurrence of the illness negatively affects patients' daily lives and increases their risks for poor health and suicide. An ideal maintenance treatment for bipolar disorder is relatively simple to take, prevents recurrence of both manic and depressive episodes, and is well-tolerated over the long term. Although many different types of medications are used for maintenance therapy of bipolar disorder, none can be considered ideal for a majority of people with bipolar disorder, and each specific form of therapy has different strengths and limitations. Clinicians need to be aware of unique efficacy and side effect factors when choosing long-term therapy and consider treatment components, goals, and individual patient characteristics, which are essential to the successful long-term management of bipolar disorder. Additionally, several forms of psychotherapy specifically tailored to the needs of people with bipolar disorder should be considered as an adjunct to medication.

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Bipolar disorder is a debilitating mental illness for which no curative treatment is currently available, making long-term symptom control necessary. Recurrent episodes of depression, mania, hypomania, or mixed episodes can negatively affect patients' social and occupational functioning.[1] Moreover, complexity is the rule, not the exception, in bipolar disorder, and comorbid psychiatric and medical difficulties frequently complicate the management plan.[1] In addition to morbidity, bipolar disorder is associated with significant mortality, and people with bipolar disorder have a higher risk of attempted and completed suicide than do those with major depressive disorder.[2,3]

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An ideal maintenance treatment for bipolar disorder would be an effective acute-phase therapy of both manic and depressive symptoms, be well-tolerated over the long term, and prevent both depressive and manic relapses. Selecting and implementing a successful long-term management plan for bipolar disorder begins with being able to weigh the strengths and limitations of the various existing maintenance treatment strategies, including psychotherapy, in the context of the goals and risks of the individual patient.

COMPONENTS OF MAINTENANCE TREATMENT

Effective Pharmacotherapies

Long-term management for bipolar disorder requires choosing a medication or combination of medications that will delay or prevent both manic and depressive episodes. Because some medications are more successful at treating or preventing one pole or the other of bipolar illness, combination therapies are frequently used instead of monotherapy. The cornerstone of therapy is a mood stabilizer. For many years, this functional category was limited to 3 medications—lithium, divalproex, and carbamazepine. However, many experts now consider lamotrigine and at least several atypical antipsychotics to be mood stabilizers. Often, the initial selection of a mood stabilizer occurs during an acute episode of illness. In this regard, lithium, divalproex, carbamazepine, and most of the atypical antipsychotics are believed to be more efficacious in the treatment of manic episodes, whereas lamotrigine is believed to be more efficacious for treatment of depressive episodes.[4] Nevertheless, despite widespread use of

lamotrigine for treatment of bipolar depression, it has approval from the U.S. Food and Drug Administration (FDA) only for maintenance phase therapy, and a meta-analysis of controlled studies of lamotrigine demonstrated relatively small effects over the placebo comparison group.[4] Among the various medications approved by the FDA for acute phase therapy of mania, only the atypical antipsychotic quetiapine is also approved for acute phase therapy of bipolar depressive episodes. Although the combination of olanzapine and fluoxetine also is approved for treatment of bipolar I depressive episodes, this combination of medication would not be used to treat mania.

If the patient responds to acute treatment with one of these strategies alone, that medication is typically continued into the maintenance phase as a monotherapy; if not, the current standard of practice is to continue treatment with the first mood stabilizer and add a second medication to try to achieve the desired response. If the second medication is not effective, a third medication is either added or substituted, and this iterative process continues until an acceptable response is achieved. No consensus of opinion exists about how long to continue these complex regimens, and, not surprisingly, increasing numbers of people with bipolar disorder are being treated with as many as 3, 4, and 5 drug regimens.[5,6]

Effective maintenance therapy is especially crucial for preventing depressive episodes because of the risk of suicide. Although it is likely that all effective maintenance-phase therapies reduce the ultimate risk of suicide by decreasing the likelihood of new episodes of illness, only lithium—the first mood stabilizer—has been empirically demonstrated to reduce the likelihood of suicidal behavior and the number of completed suicides.[2,7]

Long-Term Tolerability

As a greater number of medications have become available for the treatment of bipolar disorder, a larger number of options exist for patients who either do not benefit from or cannot tolerate older options such as lithium and divalproex. Because multiple efficacious treatment options exist, clinicians may be able to make a medication selection on the basis of long-term tolerability rather than just efficacy.[8] Continuous monitoring of tolerability is important because people who have difficulty tolerating medication side effects are more likely to discontinue therapy and because side effects such as increased appetite and excessive urination, which can be bothersome in the short-term, may have potentially dangerous long-term consequences.[9] The increasing use of the atypical antipsychotics for both acute- and longer-term therapy of bipolar disorder has helped to foster greater awareness of the longer-term risks of metabolic side effects, including weight gain, obesity, dyslipidemia, and type 2 diabetes.[9] Fortunately, early weight gain is a good predictor of subsequent risk, and careful monitoring such as measuring body weight and belt/dress size can prevent or lessen the severity of possible metabolic consequences. Dietary counseling, exercise, and targeted concomitant therapies with agents such as topiramate, sibutramine, and metformin may help some patients to minimize metabolic consequences.[10] Of course, efficacy is only part of the story, and clinicians should be prepared to switch to another medication when adverse events outweigh the benefits of a particular treatment for a given patient.[11]

Acceptable Costs of Treatment

The cost of treatment includes not only the price of the medication and the providers' services, but also the cost of long-term side effects. Some side effects of medication for bipolar disorder, such as mild parkinsonism, nausea, or sedation, may not be medically significant and can be managed by the clinician, while other adverse events, such as metabolic syndrome, may lead to life-threatening illnesses such as diabetes or cardiovascular disease.[12] Financial costs also include the expenses of performing laboratory tests and managing side effects.[13] Ineffective or intolerable treatment can lead to expensive consequences. If the costs of a particular treatment regimen outweigh the benefits, an alternative treatment should be considered.

Psychoeducation

Psychoeducation is a fundamentally important component of maintenance therapy because people who better comprehend their illness and its treatment typically become more involved in their care and can make more informed choices. The purposes of psychoeducation are to provide information and support to the patient and his or her family, prevent recurrences and suicidal behavior, improve overall functioning, offer ways to cope with symptoms, and improve quality of life.[14] Although psychoeducation can be performed within medication management sessions, the potential to learn from others' experiences should not be overlooked, particularly within the context of a supportive group process. For example, in a 2-year study, Colom and colleagues[15] examined the efficacy of group psychoeducation in 50 patients with remitted bipolar I disorder. The study found that those who attended group psychoeducation sessions ($N = 25$) had significantly fewer recurrences ($p < .01$) and a longer time to relapse than did those who attended a supportive therapy group that did not include psychoeducation ($N = 25$).

Bipolar illness typically begins relatively early in life and many people must deal with the prospect of having to begin maintenance therapy long before they reach their 25th birthday. Many younger patients with bipolar disorder discontinue therapy without talking to their doctors, often as an attempt, however misguided, to exert autonomy over the illness (i.e., "If I don't take the medication, I don't have the disease"). Discussing thoughts and feelings about having to remain on maintenance therapy, whether

in a medication monitoring session, a group of peers, or a formal psychotherapy session, can help to validate the experience and may help the individual come to terms with the personal choice element of the benefit-risk calculation. As part of psychoeducation, it is helpful to describe maintenance treatment as being *indefinite* as opposed to *lifelong*. Beyond helping to make the prospects of taking medication less onerous, the term *indefinite* also may be more accurate than *lifelong* because, although no cure for bipolar disorder exists currently, as knowledge about the neurobiology of bipolar disorder advances, new treatments may be developed that will obviate the need for lifelong treatment.

GOAL OF MAINTENANCE TREATMENT

The first goal of maintenance treatment is to prevent relapse. Unlike the usual case for management of major depressive disorder, long-term treatment should be seriously considered after stabilization of the first manic episode because the prevention of relapse early in the course of illness may lead to a more benign overall course. Studies[16–18] have found that discontinuing maintenance treatment with lithium and other drugs led to increased recurrence compared with continuing treatment; risk of relapse was especially high in the first year after discontinuation.

Certain patients have a higher risk of relapse than others and should be more closely monitored during maintenance therapy. For example, the Systematic Treatment Enhancement Program for Bipolar Disorder (STEP-BD) study[19] found that patients with an existing substance use problem had an escalated risk of recurrence of manic symptoms, while patients with an existing anxiety disorder or a lifetime eating disorder had a higher risk of recurrence of depressive symptoms. In addition, the presence of residual manic or depressive symptoms at recovery was associated with risk of relapse. Another study[20] found that obese patients had a shorter time to recurrence, had more episodes of mania and depression, and experienced more severe episodes than nonobese patients.

Nonadherence to prescribed treatment is a serious hindrance to effective relapse prevention. One study[21] of patients receiving long-term treatment with mood stabilizers found that nearly 50% of participants (46 of 98) were nonadherent to medication at some point during the previous 2-year period, and almost one third of patients (29 of 92) missed 30% or more of their medication in the previous month. Nonadherence may be due to multiple factors, including youth, substance use, side effects of medication, unwillingness to give up elevated moods, and overall negative feelings about taking medication and having a chronic mental illness.[22,23] In an effort to increase adherence to treatment, clinicians should maintain a supportive alliance with patients and inquire about adherence and patients' expectations of treatment.[24] Patients and their families should be encouraged to consult the clinician if problems arise due to their medication.

EFFICACY OF MAINTENANCE TREATMENTS

Lithium

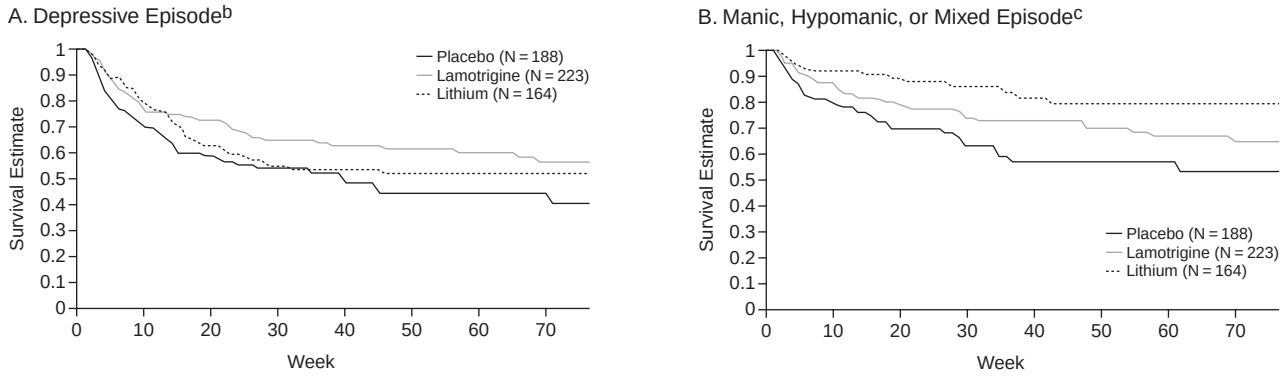
Lithium continues to be the standard of comparison for all new therapies.[25] Lithium became the first medication approved for maintenance treatment of bipolar disorder in 1974, and over 40 years of data support its preventive efficacy. In a review of 5 randomized controlled trials (N = 770), Geddes and colleagues[26] found that lithium treatment decreased the likelihood that patients would relapse from 61% to 40% and was especially effective in preventing manic episodes.

Although there is no doubt about the maintenance-phase efficacy of lithium therapy for bipolar disorder, clear limitations exist: among patients participating in contemporary treatment studies, lithium therapy may fail more often than it succeeds; the cumulative burden of certain side effects and complications, such as hypothyroidism, decreasing kidney function, cognitive impairment, and tremor, slowly builds over the years; and only about one third of people who benefit from lithium therapy remain on the medication indefinitely. For example, Maj and colleagues[27] found that the long-term efficacy of lithium therapy was difficult to measure because adherence to the medication was low. After 5 years, of 402 enrolled patients, 27.9% were no longer taking lithium, 38.1% were still taking lithium but had experienced at least 1 recurrence, 23.4% were still taking lithium and had experienced no recurrence, and 10.7% were unavailable. Patients whose blood lithium levels were at therapeutic values more than 90% of the time experienced substantially greater benefit than patients who had more frequent subtherapeutic blood levels. Many side effects are dose related and can be reduced or eliminated, but some patients simply cannot tolerate or will not take lithium.[28] Side effects of lithium may include constant need to urinate, thirst, weight gain, cognitive problems, hand tremors, gastrointestinal problems, hair loss, acne, water retention, hypothyroidism, and possible kidney damage.[28]

Valproate

Following the FDA approval of divalproex for acute treatment of mania in 1994, it relatively rapidly became a first-choice treatment, and the use of lithium began to decline.[7] Within 1 decade, lithium went from being almost universally used for the treatment of bipolar disorder to being only occasionally used. Valproate is an effective treatment for mania, but the case for its widespread use ahead of lithium is relatively weak, and valproate is not FDA approved for the maintenance phase of bipolar disorder. Macritchie and colleagues[29] reviewed multiple randomized controlled trials examining the efficacy of

Figure 1. Time to Recurrence for (A) Depressive Episode and (B) Manic, Hypomanic, or Mixed Episode (Kaplan-Meier Survival Curves)[a]



[a]Reprinted with permission from Goodwin et al.[36] Mean lamotrigine dosage was 245 mg/day and mean serum lithium level was 0.7 mEq/L. Median time to intervention for depression (95% CI) was 270 days (138 to not calculable) for placebo; these values were not calculable for the lithium or lamotrigine group.
[b]Lamotrigine versus placebo, p = .009; lithium versus placebo, p = .120; lamotrigine versus lithium, p = .325.
[c]Lamotrigine versus placebo, p = .34; lithium versus placebo, lamotrigine versus lithium, p = .030.

valproate and concluded that the shift from lithium to valproate was not supported by sufficient evidence. Bowden et al.[30] compared the efficacy of divalproex maintenance treatment with that of lithium and placebo. Interpretation of this 12-month study was confounded by a remarkably low relapse rate in the group receiving placebo and found that time to recurrence of any mood episode did not differ statistically among the 3 treatment groups. Secondary analyses of this study did find evidence supporting the efficacy of valproate on several indices, including prevention of depressive relapses.[31] Revicki et al.[32] examined the effectiveness and costs of treatment for bipolar I disorder with divalproex or lithium for 1 year (N = 201). No statistical differences were found between groups for clinical symptoms, quality of life outcomes, or disability days, but discontinuation due to lack of efficacy or adverse effects was lower among patients taking divalproex (12%) than lithium (23%). Goodwin and colleagues[7] measured the risk of suicide in patients taking lithium versus divalproex and found that the rate of suicide death was 2.7 times higher (95% CI = 1.1 to 6.3; p = .03) in patients who were taking divalproex than in those who were taking lithium. Nonfatal attempts were also higher with divalproex.

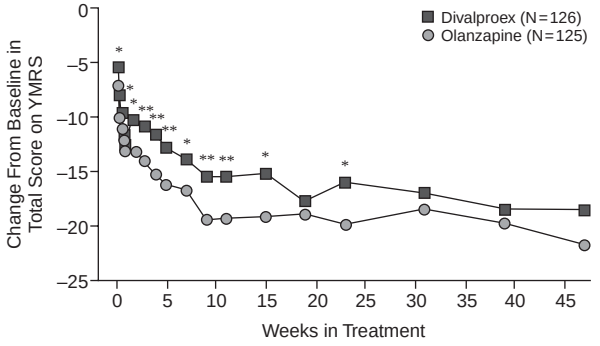
Perhaps valproate's greatest strength is that it can be both effective and well-tolerated in patients who do not respond well to lithium, including those presenting in mixed episodes or with a history of rapid cycling.[33] Common side effects of divalproex include weight gain, sedation, hair loss, and gastrointestinal distress; less common side effects include development of polycystic ovary syndrome, thrombocytopenia, and, more rarely, liver and pancreatic dysfunction.[28] However, divalproex has a larger therapeutic window than lithium, and side effects may be lessened with dosage adjustments.

Lamotrigine

In 2003, lamotrigine received an FDA indication for maintenance treatment of bipolar disorder. As lamotrigine does not have an indication for treatment of acute mania or depression, it is the only treatment in psychiatry that is approved to prevent an illness that it has not been proven to treat during the acute phase. The FDA approval was based on two 18-month double-blind trials[34,35]; one[34] enrolled bipolar I patients who were recovering from manic episodes and the other[35] enrolled bipolar I patients who were recovering from depressive episodes. Goodwin et al.[36] reported on the efficacy of lamotrigine and lithium monotherapies versus placebo in a pooled analysis of these studies. They found that both lamotrigine and lithium were superior to placebo for lengthening the time to a mood episode. However, the 2 active therapies were differentially effective, and, whereas lithium was superior to lamotrigine for prevention of mania, the converse was true for prevention of depressive episodes (Figure 1). For this reason, many clinicians use lamotrigine in combination with lithium, divalproex, or other mood stabilizers for patients with a history of multiple prior manic episodes.

Lamotrigine is generally a well-tolerated medication and, among mood stabilizers, is the only one to have minimal rates of both sedation and weight gain. The single major limitation is that, depending on the study, between 5% and 10% of patients treated with lamotrigine will develop a skin rash, and it is impossible to predict whether the rash will run a benign course or develop into a systemic allergic reaction such as Stevens-Johnson syndrome. As such, all patients treated with lamotrigine must be instructed to stop therapy immediately at the first sign of a rash, which means that—given the incidence of rash—up to 1 in 10 people treated with lamotrigine will have the

Figure 2. Change From Baseline in Mean Total Score on YMRS With Olanzapine or Divalproex for Mania[a]



[a]Reprinted with permission from Tohen et al.[39]At week 47, the numbers of subjects were 19 for olanzapine and 21 for divalproex.
*Significant difference between groups ($p < .05$, mixed model repeated-measures analysis of variance).
**Significant difference between groups ($p < .01$, mixed model repeated-measures analysis of variance).
Abbreviation: YMRS = Young Mania Rating Scale.

course of therapy suspended. To minimize this risk, lamotrigine therapy is initiated at a very low dose (typically 25 mg/day or only about one eighth of the usual therapeutic dose) and titrated very slowly. Additional caution is needed when combining lamotrigine with valproate, which slows metabolism and essentially doubles blood lamotrigine levels.

Atypical Antipsychotics

In 2004, olanzapine became the first atypical antipsychotic to be approved for the maintenance treatment of bipolar disorder, followed by aripiprazole in 2005 and quetiapine in 2008. The FDA approval of olanzapine was based on several controlled studies, including a placebo-controlled, 48-week study[37] using a discontinuation design after acute-phase stabilization on olanzapine monotherapy and a second 52-week, double-blind study[38] comparing olanzapine and lithium monotherapies after acute-phase stabilization on the combination of the 2 drugs. The first study[37] found that olanzapine-treated patients had significantly longer time to relapse to any mood episode than placebo-treated patients (median = 174 days vs. 22 days; $p < .001$). The second study[38] found that fewer olanzapine-treated patients experienced recurrence of manic or mixed episodes than lithium-treated patients (30% vs. 38%), and time until recurrence, which was defined as meeting the *Diagnostic and Statistical Manual of Mental Disorders*, Fourth Edition (DSM-IV) criteria, was significantly longer for those treated with olanzapine ($p = .040$).

To compare the efficacy of olanzapine and divalproex for long-term treatment of bipolar disorder, Tohen and colleagues[39] conducted a 47-week, randomized, double-blind study. Participants in manic or mixed episodes at study entry (N = 251) were given olanzapine (5–20 mg/day) or divalproex (500–2500 mg/day); adjunctive lorazepam was also allowed to treat agitation. The Young Mania Rating Scale (YMRS) was used to measure efficacy (≥ 20 total score for inclusion, ≤ 12 for remission, and ≥ 15 for relapse). Across the 47 weeks, the olanzapine group experienced significantly greater mean improvement in YMRS total scores than patients given divalproex (Figure 2). Additionally, the median time to remission of manic symptoms was significantly shorter for those in the olanzapine group (14 days vs. 62 days). Side effects with olanzapine were increased appetite, weight gain, somnolence, dry mouth, akathisia, and elevated liver function test results.

To measure the efficacy and tolerability of aripiprazole for maintenance therapy in bipolar I disorder, Keck et al.[40] conducted a 100-week, randomized, double-blind, placebo-controlled study. Participants in manic or mixed episodes at study entry were stabilized with aripiprazole treatment (15–30 mg/day). Those who achieved stabilization (N = 161) according to the YMRS (≤ 10 total score) and Montgomery-Asberg Depression Rating Scale (≤ 13 total score for 6 consecutive weeks) were given aripiprazole or placebo for 26 weeks. Patients who completed the 26-week phase without a relapse were allowed to continue treatment for 74 weeks. By the final week of the study, the time to relapse of any mood episode was significantly longer with aripiprazole than with placebo. Although aripiprazole was superior to placebo in increasing time to manic relapse, it was not significantly superior to placebo in increasing time to depressive relapse (Figure 3). Side effects with aripiprazole were dry mouth, hypertension, weight gain, tremor, akathisia, abnormal thinking, pharyngitis, and flu syndrome.

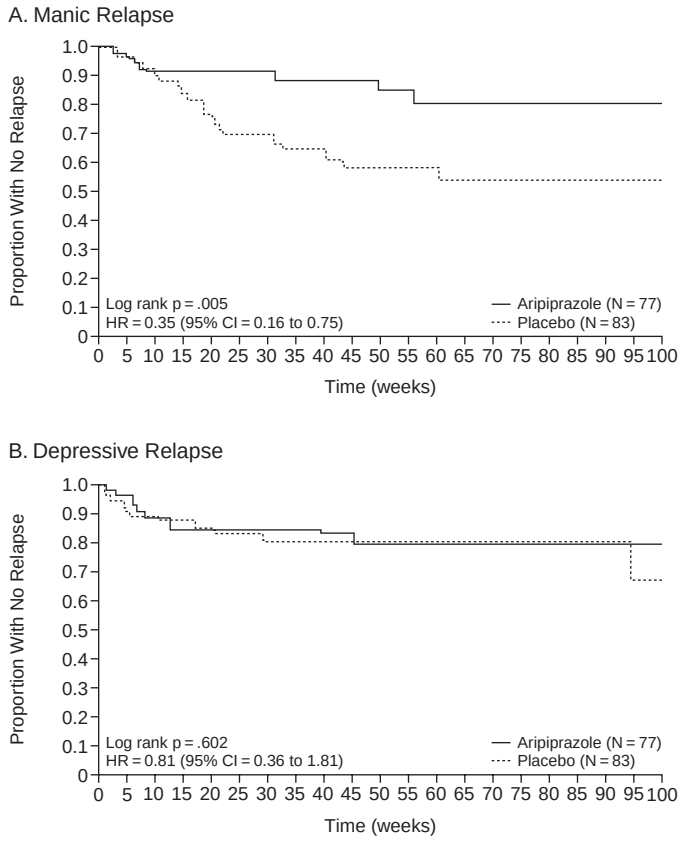
The efficacy of quetiapine also has recently been established as maintenance therapy, leading to FDA approval for this indication. However, because the pivotal studies that led to this recent approval have not yet been published, it is not possible to include the data in this review.

Clinicians should consider the possible serious side effects of atypical antipsychotics when contemplating risks versus benefits. These side effects should not prevent use but should be closely monitored by clinicians. For instance, patients' waist size and fasting glucose level should be monitored early in the course of treatment with olanzapine, and if clinicians intervene when appropriate to lessen metabolic consequences, patients may have better outcomes.

Antidepressants

Patients with bipolar disorder experience more days of depressive symptoms than manic or hypomanic symptoms. Judd et al.[41] measured the number of weeks that patients with bipolar I disorder (N = 146) spent manic or hypomanic, depressed, in mixed states or with rapid cycling, or asymptomatic. Patients experienced mood symptoms 47.3% of the time during a 12.8-year follow-up

Figure 3. Time to (A) Manic Relapse and (B) Depressive Relapse (Kaplan-Meier Survival Curves)[a]



[a]Reprinted with permission from Keck et al.[40]
Abbreviation: HR = hazard ratio.

period. When experiencing mood symptoms, patients spent over 3 times more weeks depressed than manic. A second study[42] of patients with bipolar II disorder (N = 86) found that patients experienced mood symptoms 53.9% of the time during a 13.4-year follow-up period. Depressive symptoms occurred during 50.3% of all follow-up weeks.

Because depression can dominate the course of bipolar disorder for many patients, the use of antidepressants for long-term treatment seems logical. However, no expert consensus supports this conclusion. Some experts recommend a short, finite duration of antidepressant therapy, such as 3 to 6 months after remission, while others recommend indefinite use in patients who respond well to antidepressants in conjunction with other medication.[43] Antidepressant monotherapy generally should be avoided for patients with bipolar I disorder because these medications provide no protection against mania and, for a vulnerable subgroup of patients, may accelerate episode cyclicity.[43]

No properly controlled studies support maintenance phase antidepressant therapy using the modern antidepressants. Altshuler and colleagues[43] measured the risk of depressive relapse over 1 year in a retrospective study of 44 patients who were taking mood stabilizers and were treated for acute depressive episodes with antidepressants. After stabilization, 19 patients continued taking the antidepressants, while 25 patients discontinued antidepressant treatment. As this was not a randomized study, the decision to continue on antidepressant treatment or to discontinue was based on the judgment of the doctor-patient team. After 1 year, 68% of patients who discontinued antidepressants had relapsed, and 32% of patients who continued antidepressants had relapsed (p = .0065). These data suggest that ongoing antidepressant therapy may be beneficial for a subset of bipolar patients. When depression prophylaxis is the primary goal of treatment, lamotrigine should also be considered as a viable alternative to antidepressants.[36]

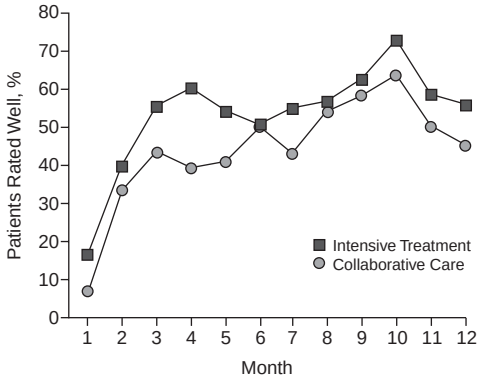
Combined Therapy

Most patients are treated with a combination of medications. For example, Post et al.[5] followed outpatients treated as part of the Stanley Foundation Bipolar Network for 1 year. The 258 patients were taking an average of 4.1 psychotropic medications. A single medication is ideal because adjunctive medications may increase side effects and cause drug interactions, thus increasing the risk of nonadherence to treatment.[44] However, combination treatment can provide added benefit and may be needed for long-term treatment, as monotherapy may have limited efficacy against preventing both mania and depression.

An 18-month study[45] examined recurrence prevention in bipolar I disorder with combination treatment with olanzapine plus a mood stabilizer versus monotherapy with a mood stabilizer alone. The DSM-IV criteria were used to measure syndromal relapse, while the YMRS and the Hamilton Rating Scale for Depression were used to measure symptomatic relapse. Participants were stabilized on treatment with olanzapine and either lithium or valproate and then were treated with lithium or valproate plus either olanzapine or placebo. The median time to any symptomatic relapse was significantly longer for participants who remained on combination therapy (163 days) than those who switched to mood stabilizer monotherapy (42 days; p = .023). However, no significant difference was found between groups in median time to any syndromal relapse (94 days for combination therapy vs. 40 for monotherapy).

Although the FDA-approved combination therapies for the treatment of acute manic states and acute bipolar depression, few of the combinations available to psychiatrists for maintenance-phase therapy in the 21st century

Figure 4. Proportion of Patients Rated Well With Intensive Psychosocial Treatment or Collaborative Care[a,b]



[a]Reprinted with permission from Miklowitz et al.[47]
[b]p = .003.

have been systematically studied. Despite this absence, combination therapy is commonly used for maintenance treatment.[46] Ketter and colleagues[46] suggested combining mood stabilizers with second-generation antipsychotics or antidepressants with second-generation antipsychotics to improve outcomes for treatment-resistant patients. However, no sufficient data support the efficacy of one combination over another.[33] More research on using 2 or more medications in the maintenance phase is needed.[28,44]

PSYCHOTHERAPY IN MAINTENANCE TREATMENT

Historically, the efficacy of psychotherapy in the long-term management of bipolar disorder has been discounted, which is partially due to the recognition of bipolar disorder as a stronger neurobiological illness than other forms of depression. However, recent evidence has emerged supporting the efficacy of various kinds of focused psychotherapies in patients with bipolar disorder.

A trial from the STEP-BD study[47] examined the effects of pharmacotherapy combined with intensive psychotherapy or collaborative care on the risk of recurrence of bipolar episodes. Patients were given appropriate pharmacotherapy with mood stabilizers (plus or minus antidepressants) and were randomly assigned to 1 of the 3 groups of intensive psychotherapy (N = 163) or collaborative care (N = 130). The 3 forms of psychotherapy studied were family-focused therapy, cognitive-behavioral therapy (CBT), and interpersonal-social rhythm therapy; each had been shown to have significant effects in at least one prior study. After 1 year, recovery rates were significantly higher for the intensive psychotherapy groups than for the collaborative care group (64.4% vs. 51.5%; p = .01). Intensive psychotherapy groups also had a significantly shorter time to recovery (p = .01) and were more likely to be well during any month of the study than the collaborative care group (Figure 4). No significant differences in outcomes between intensive psychotherapy groups were found, although the necessity of having an involved significant other decreased the acceptability of family-focused therapy compared to CBT or interpersonal-social rhythm therapy. Thus, when combined with pharmacotherapy, intensive psychotherapy may increase the likelihood that bipolar patients will recover and stay well. The value of focused psychotherapy for maintenance treatment of bipolar disorder should not be minimized.

CONCLUSION

Because bipolar disorder is often a lifelong illness that can have life-ruining consequences, the ultimate goal of treatment is the prevention of episode recurrences through the long-term management of symptoms. To effectively control the illness, clinicians must develop and adjust a maintenance treatment plan while sustaining a supportive relationship with the patient in order to promote adherence. Multiple medications are used for long-term treatment of bipolar disorder, although no cure is available. Despite the introduction of numerous therapies in recent years, lithium should continue to be thought of as a first-line treatment, and it remains one of the standards of comparison. Atypical antipsychotics are also being used fairly early in treatment, either as monotherapy or to augment mood stabilizers. Antidepressants may be efficacious as adjunctive treatment for a subgroup of patients, but there is no consensus regarding duration of their use. Lamotrigine is a viable alternative to antidepressants for maintenance-phase therapy. Side effects of any medication should be closely monitored throughout the maintenance period. In addition, psychotherapy should be considered as an adjunct to medication, as recent evidence supports its efficacy for maintenance therapy for bipolar disorder.

Drug names: aripiprazole (Abilify), carbamazepine (Tegretol, Equetro, and others), divalproex (Depakote and others), lamotrigine (Lamictal and others), lithium (Lithobid, Eskalith, and others), lorazepam (Ativan and others), metformin (Glucophage, Riomet, and others), olanzapine (Zyprexa), olanzapine-fluoxetine combination (Symbyax), quetiapine (Seroquel), sibutramine (Meridia), topiramate (Topamax).

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

REFERENCES

1. Calabrese JR, Hirschfeld RMA, Reed M, et al. Impact of bipolar disorder on a US community sample. J Clin Psychiatry 2003;64:425–432
2. Baldessarini R, Pompili M, Tondo L. Suicide in bipolar disorder: risks and management. CNS Spectr 2006;11:465–471
3. Rihmer Z, Kiss K. Bipolar disorders and suicidal behaviour. Bipolar Disord 2002;4(suppl 1):21–25
4. Calabrese JR, Shelton MD, Rapport DJ, et al. Long-term treatment of bipolar disorder with lamotrigine. J Clin Psychiatry 2002;63(suppl 10):18–22
5. Post RM, Denicoff KD, Leverich GS, et al. Morbidity in 258 bipolar

outpatients followed for 1 year with daily prospective ratings on the NIMH life chart method. J Clin Psychiatry 2003;64:680–690
6. Ghaemi SN, Hsu DJ, Thase ME, et al. Pharmacological treatment patterns at study entry for the first 500 STEP-BD participants. Psychiatr Serv 2006;57: 660–665
7. Goodwin FK, Fireman B, Simon GE, et al. Suicide risk in bipolar disorder during treatment with lithium and divalproex. JAMA 2003;290:1467–1473
8. Dunner DL. Safety and tolerability of emerging pharmacological treatments for bipolar disorder. Bipolar Disord 2005;7:307–325
9. Masand PS, Fazal FS, Patkar AA. Safety considerations in pharmacotherapy of bipolar disorder. CNS Spectr 2004;9(11,suppl 12):16–26
10. Baptista T, Elfakih Y, Uzcategui E, et al. Pharmacological management of atypical antipsychotic-induced weight gain. CNS Drugs 2008;22:477–495
11. Young AH. Treatment of bipolar disorder with antipsychotic medication: issues shared with schizophrenia. J Clin Psychiatry 2007;68(suppl 6):24–25
12. Newcomer JW. Medical risk in patients with bipolar disorder and schizophrenia. J Clin Psychiatry 2006;67(suppl 9):25–30
13. Leonard BE. Clinical trials and their importance in assessing the efficacy and safety of psychotropic drugs. In: Leonard BE. Fundamentals of Psychopharmacology. 3rd ed. Chichester, United Kingdom: John Wiley and Sons; 2003: 101–111
14. Colom F, Vieta E, Martinez A, et al. What is the role of psychotherapy in the treatment of bipolar disorder? Psychother Psychosom 1998;67:3–9
15. Colom F, Vieta E, Reinares M, et al. Psychoeducation efficacy in bipolar disorders: beyond compliance enhancement. J Clin Psychiatry 2003;69: 1101–1105
16. Baldessarini RJ, Tondo L. Recurrence risk in bipolar manic-depressive disorders after discontinuing lithium maintenance treatment: an overview. Clin Drug Invest 1998;15:337–351
17. Biel MG, Peselow E, Mulcare L, et al. Continuation versus discontinuation of lithium in recurrent bipolar illness: a naturalistic study. Clin Drug Investig 1998;15:337–351
18. Cavanagh J, Smyth R, Goodwin GM. Relapse into mania or depression following lithium discontinuation: a 7-year follow-up. Acta Psychiatr Scand 2004;109:91–95
19. Perlis RH, Ostacher MJ, Patel JK, et al. Predictors of recurrence in bipolar disorder: primary outcomes from the Systematic Treatment Enhancement Program for Bipolar Disorder (STEP-BD). Am J Psychiatry 2006;163: 217–224
20. Fagiolini A, Kupfer DJ, Houck PR, et al. Obesity as a correlate of outcome in patients with bipolar I disorder. Am J Psychiatry 2003;160:112–117
21. Scott J, Pope M. Nonadherence with mood stabilizers: prevalence and predictors. J Clin Psychiatry 2002;63:384–390
22. Baldessarini RJ, Perry R, Pike J. Factors associated with treatment nonadherence among US bipolar disorder patients. Hum Psychopharmacol 2008; 23(suppl 2):95–105
23. Pope M. Do clinicians understand why individuals stop taking lithium? J Affect Disord 2003;74:287–291
24. Gaudiano BA, Miller IW. Patients' expectancies, the alliance in pharmacotherapy, and treatment outcomes in bipolar disorder. J Consult Clin Psychol 2006;74:671–676
25. Muzina DJ, Calabrese JR. Maintenance therapies in bipolar disorder: focus on randomized controlled trials. Aust N Z J Psychiatry 2005;39:652–661
26. Geddes JR, Burgess S, Hawton K, et al. Long-term lithium therapy for bipolar disorder: systematic review and meta-analysis of randomized controlled trials. Am J Psychiatry 2004;161:217–222
27. Maj M, Pirozzi R, Maglianp L, et al. Long-term outcome of lithium prophylaxis in bipolar disorder: a 5-year prospective study of 402 patients at a lithium clinic. Am J Psychiatry 1998;155:30–35
28. National Alliance of the Mentally Ill. About Mental Illness. Available at: http://www.nami.org/Template.cfm?Section = By_Illness&Template = /TaggedPage/TaggedPageDisplay.cfm&TPLID = 54&ContentID = 23037&lstid = 325. Accessed May 8, 2008
29. Macritchie KA, Geddes JR, Scott J, et al. Valproic acid, valproate and divalproex in the maintenance treatment of bipolar disorder. Cochrane Database Syst Rev 2001;3:CD003196
30. Bowden CL, Calabrese JR, McElroy SL, et al. A randomized, placebo-controlled 12-month trial of divalproex and lithium in treatment of outpatients with bipolar I disorder. Arch Gen Psychiatry 2000;57:481–489
31. Gyulai L, Bowden CL, McElroy SL, et al. Maintenance efficacy of divalproex in the prevention of bipolar depression. Neuropsychopharmacology 2003;28: 1374–1382
32. Revicki DA, Hirschfeld RM, Ahearn EP, et al. Effectiveness and medical costs of divalproex versus lithium in the treatment of bipolar disorder: results of a naturalistic clinical trial. J Affect Disord 2005;86:183–193
33. American Psychiatric Association. Practice Guideline for the Treatment of Patients With Bipolar Disorder [Revision]. Am J Psychiatry 2002; 159(suppl 4):1–50
34. Bowden CL, Calabrese JR, Sachs G, et al. A placebo-controlled 18-month trial of lamotrigine and lithium maintenance treatment in recently manic or hypomanic patients with bipolar I disorder. Arch Gen Psychiatry 2003;60: 392–400. Correction 2004;61:680
35. Calabrese JR, Bowden CL, Sachs G, et al, for the Lamictal 605 Study Group. A placebo-controlled 18-month trial of lamotrigine and lithium maintenance treatment in recently depressed patients with bipolar I disorder. J Clin Psychiatry 2003;64:1013–1024
36. Goodwin GM, Bowden CL, Calabrese JR, et al. A pooled analysis of 2 placebo-controlled 18-month trials of lamotrigine and lithium maintenance in bipolar I disorder. J Clin Psychiatry 2004;65:432–441
37. Tohen M, Calabrese JR, Sachs GS, et al. Randomized, placebo-controlled trial of olanzapine as maintenance therapy in patients with bipolar I disorder responding to acute treatment with olanzapine. Am J Psychiatry 2006;163: 247–256
38. Tohen M, Greil W, Calabrese JR, et al. Olanzapine versus lithium in the maintenance treatment of bipolar disorder: a 12-month, randomized, double-blind, controlled clinical trial. Am J Psychiatry 2005;162:1281–1290
39. Tohen M, Ketter TA, Zarate CA, et al. Olanzapine versus divalproex sodium for the treatment of acute mania and maintenance of remission: a 47-week study. Am J Psychiatry 2003;160:1263–1271
40. Keck PE Jr, Calabrese JR, McIntyre RS, et al. Aripiprazole monotherapy for maintenance therapy in bipolar I disorder: a 100-week, double-blind study versus placebo. J Clin Psychiatry 2007;68:1480–1491
41. Judd LL, Akiskal HS, Schettler PJ, et al. The long-term natural history of the weekly symptomatic status of bipolar I disorder. Arch Gen Psychiatry 2002;59:530–537
42. Judd LL, Akiskal HS, Schettler PJ, et al. A prospective investigation of the natural history of the long-term weekly symptomatic status of bipolar II disorder. Arch Gen Psychiatry 2003;60:261–269
43. Altshuler L, Kiriakos L, Calcagno J, et al. The impact of antidepressant discontinuation vs antidepressant continuation on 1-year risk for relapse of bipolar disorder. J Clin Psychiatry 2001;62:612–616
44. Goodwin G, Vieta E. Effective maintenance treatment: breaking the cycle of bipolar disorder. Eur Psychiatry 2005;20:365–371
45. Tohen M, Chengappa KNR, Suppes T, et al. Relapse prevention in bipolar I disorder: 18-month comparison of olanzapine plus mood stabiliser v mood stabiliser alone. Br J Psychiatry 2004;184:337–345
46. Ketter TA. Monotherapy versus combined treatment with second-generation antipsychotics in bipolar disorder. J Clin Psychiatry 2008;69(suppl 5): 9–15
47. Miklowitz DJ, Otto MW, Frank E, et al. Psychosocial treatments for bipolar depression: a 1-year randomized trial from the Systematic Treatment Enhancement Program. Arch Gen Psychiatry 2007;64:419–426