

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 colleagues¹⁵ 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. Studies¹⁶⁻¹⁸ 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) study¹⁹ 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 study²⁰ 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 study²¹ 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

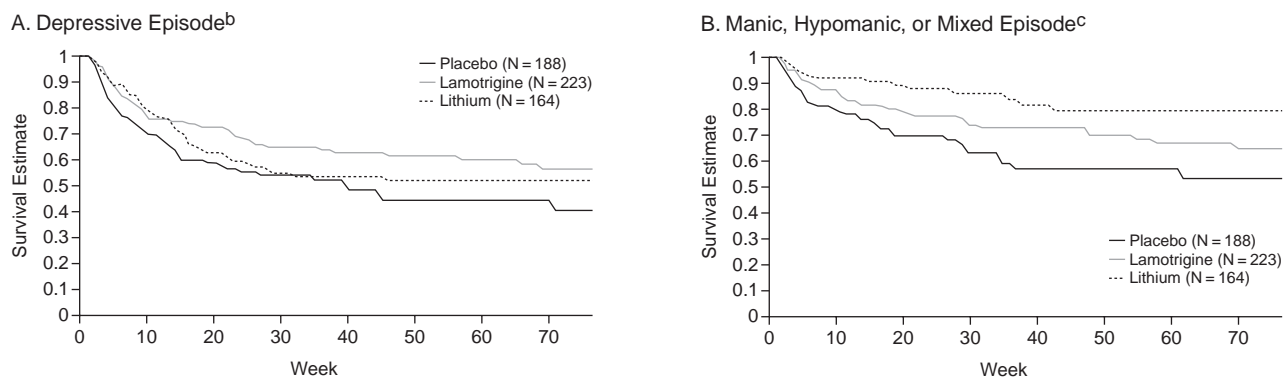
Lithium continues to be the standard of comparison for all new therapies.²⁵ Lithium became the first medication approved for maintenance treatment of bipolar disorder in 1974, and over 40 years of data support its preventive efficacy. In a review of 5 randomized controlled trials (N = 770), Geddes and colleagues²⁶ 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 colleagues²⁷ 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 colleagues²⁹ 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



^aReprinted 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.

^bLamotrigine versus placebo, $p = .009$; lithium versus placebo, $p = .120$; lamotrigine versus lithium, $p = .325$.

^cLamotrigine 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 colleagues⁷ 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.

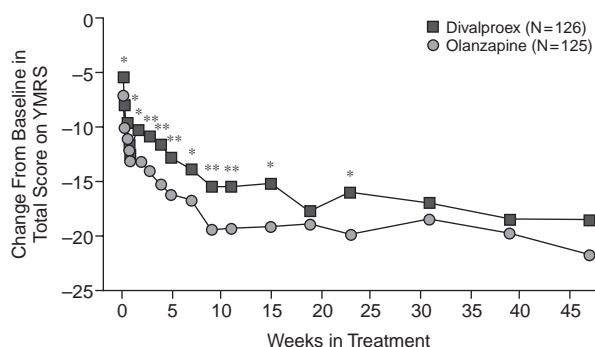
Perhaps valproate's greatest strength is that it can be both effective and well-tolerated in patients who do not respond well to lithium, including those presenting in mixed episodes or with a history of rapid cycling.³³ Common side effects of divalproex include weight gain, sedation, hair loss, and 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}; one³⁴ enrolled bipolar I patients who were recovering from manic episodes and the other³⁵ 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



^aReprinted 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 study³⁷ using a discontinuation design after acute-phase stabilization on olanzapine monotherapy and a second 52-week, double-blind study³⁸ comparing olanzapine and lithium monotherapies after acute-phase stabilization on the combination of the 2 drugs. The first study³⁷ 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 study³⁸ 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 colleagues³⁹ 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.

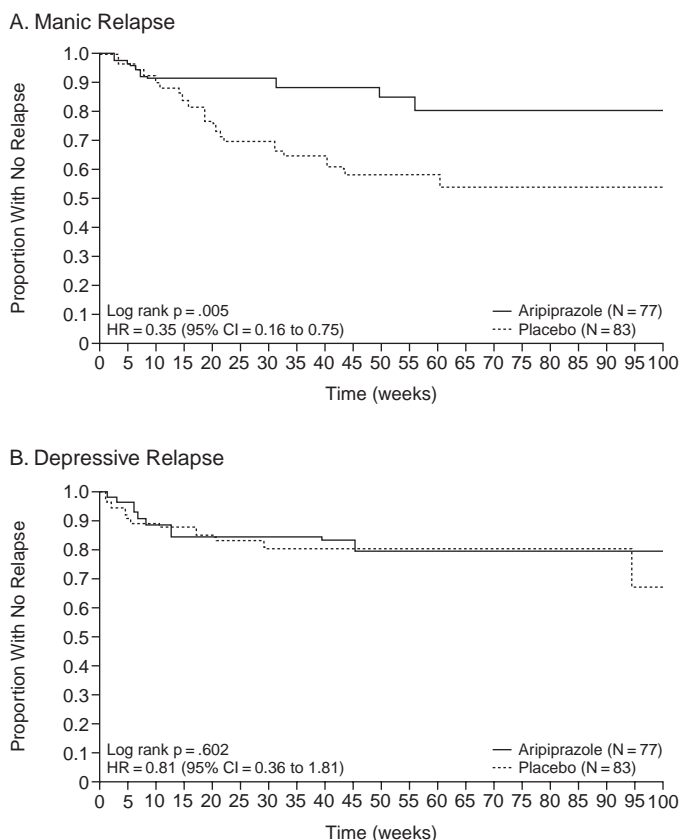
The efficacy of quetiapine also has recently been established as maintenance therapy, leading to FDA approval for this indication. However, because the pivotal studies that led to this recent approval have not yet been published, it is not possible to include the data in this review.

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



^aReprinted 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 study⁴² 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 cyclicality.⁴³

No properly controlled studies support maintenance phase antidepressant therapy using the modern antidepressants.

Altshuler and colleagues⁴³ 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 study⁴⁵ 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

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