Bipolar disorder in adults: Choosing maintenance treatment

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INTRODUCTION

Following remission of a bipolar mood episode, nearly all patients require maintenance treatment to delay or prevent another episode. Standard maintenance treatment consists of pharmacotherapy plus adjunctive psychotherapy. However, if psychotherapy is not available or is declined, pharmacotherapy alone is reasonable.

Selecting maintenance treatment for bipolar disorder is reviewed here. The use of adjunctive psychotherapy for maintenance treatment of bipolar disorder; management of poor adherence to maintenance pharmacotherapy; pharmacotherapy for acute bipolar mood episodes; teratogenic risks and neonatal issues involved in pharmacotherapy; and the epidemiology, clinical manifestations, and diagnosis of bipolar disorder are discussed separately:

- (See "Bipolar disorder in adults: Psychoeducation and other adjunctive maintenance psychotherapies".)
- (See "Bipolar disorder in adults: Managing poor adherence to maintenance pharmacotherapy".)
- (See "Bipolar mania and hypomania in adults: Choosing pharmacotherapy".)
- (See "Bipolar major depression in adults: Choosing treatment".)
- (See "Teratogenicity, pregnancy complications, and postnatal risks of antipsychotics, benzodiazepines, lithium, and electroconvulsive therapy".)
- (See "Bipolar disorder in adults: Epidemiology and pathogenesis".)

- (See "Bipolar disorder in adults: Clinical features".)
- (See "Bipolar disorder in adults: Assessment and diagnosis".)

DEFINITION OF BIPOLAR DISORDER

Bipolar disorder is a mood disorder that is characterized by episodes of mania (table 1), hypomania (table 2), and major depression (table 3) [1]. The subtypes of bipolar disorder include bipolar I and bipolar II. Patients with bipolar I disorder experience manic episodes, and nearly always experience hypomanic and major depressive episodes. Bipolar II disorder is marked by at least one hypomanic episode, at least one major depressive episode, and the absence of manic episodes. Additional information about the clinical features and diagnosis of bipolar disorder is discussed separately. (See "Bipolar disorder in adults: Clinical features" and "Bipolar disorder in adults: Assessment and diagnosis", section on 'Diagnosis'.)

Recurrent mood episodes — Bipolar disorder is characterized by recurrent mood episodes that can be life-threatening. As an example, the Systematic Treatment Enhancement Program for Bipolar Disorder (STEP-BD) prospectively followed 858 patients who recovered from a mood episode, and found that within two years a recurrent episode occurred in nearly 50 percent, despite receiving treatment at specialty mood disorder clinics [2]. In addition, a meta-analysis of three studies lasting four years prospectively followed patients (n = 198) who recovered from an episode of mania and found that a recurrent mood episode occurred in 60 percent [3]. For each patient, manic and depressive episodes may recur in roughly equal proportions, or there may be a predominant polarity [4].

Recurrence of bipolar mood episodes is associated with a greater number of suicide attempts [5-9], as well as poorer social and occupational functioning [10] and cognitive impairment [11]. In addition, treatment resistance for each episode appears to increase with each additional recurrence [12,13].

INDICATIONS

We suggest maintenance pharmacotherapy for nearly every euthymic patient with bipolar disorder, and observational studies support starting maintenance pharmacotherapy early in the course of illness [14]. As an example, a registry study found that starting lithium prophylaxis after a first manic or mixed episode was more effective than starting it later, such that hospitalization occurred less often (hazard ratio 0.75, 95% CI 0.67-0.84) [14]. Other observational studies suggest that maintenance treatment is indicated after a first manic episode based upon findings that cognitive dysfunction and brain volume deficits recover only if no further episodes occur over the

course of the following year [15,16]. Adjunctive psychotherapy during maintenance treatment is also indicated for all bipolar patients to prevent relapses and enhance adherence. The goals for maintenance therapy are to reduce residual symptoms, delay and prevent recurrence of new mood episodes, reduce the risk of suicide, and improve psychosocial functioning. Maintenance pharmacotherapy for bipolar disorder is consistent with multiple practice guidelines [17-20].

Although most maintenance pharmacotherapy studies have primarily or exclusively enrolled patients with bipolar I disorder, we suggest maintenance treatment for bipolar II disorder as well. Patients with bipolar II disorder are symptomatically ill more than 50 percent of their lives following onset of the illness and are at high risk for suicide [21].

We also suggest maintenance pharmacotherapy for other specified bipolar disorder, based upon our clinical experience. Although there are no controlled trials or observational studies to guide management [17,18], the disorder is nevertheless a clinically significant syndrome that requires acute and maintenance treatment [22,23].

Suicide attempts may be minimized by maintenance therapy. An observational study of 406 patients followed for up to 22 years found that fewer suicide deaths occurred in bipolar patients who received maintenance treatment than those not treated (standardized mortality ratio 6 versus 27) [24]. Among medications used for bipolar disorder, lithium consistently has the best record for suicide prevention. (See "Suicidal ideation and behavior in adults", section on 'Pharmacotherapy'.)

In addition to preventing relapse in patients with bipolar disorder, maintenance pharmacotherapy may be associated with reduced rates of violent behavior. A national registry study identified 494 convictions for violent crime (eg, assault, robbery, or threats/intimidation) in 11,918 patients with bipolar disorder and examined the time periods when patients were or were not prescribed mood stabilizers (eg, lithium, valproate, lamotrigine, or carbamazepine) or antipsychotics [25]. The rate of violent behavior when mood stabilizers were prescribed was 60 percent less, compared with times when mood stabilizers were not prescribed (hazard ratio 0.4, 95% CI 0.3-0.7). In addition, prescription of antipsychotics was associated with a 50 percent decrease in interpersonal violence (hazard ratio 0.5, 95% CI 0.3-0.9). Additional information about violent behavior in bipolar disorder is discussed separately. (See "Bipolar disorder in adults: Clinical features", section on 'Perpetration'.)

SELECTING A TREATMENT REGIMEN

Pharmacotherapy is essential for maintenance treatment of bipolar disorder. The same medication regimen that was successfully used acutely is typically selected for maintenance

treatment. However, some medications are preferable for maintenance treatment due to their demonstrated efficacy and tolerability. (See 'Choosing pharmacotherapy' below.)

In addition, we suggest combining pharmacotherapy with psychotherapy for maintenance treatment of bipolar disorder. Multiple randomized trials indicate that adjunctive group psychoeducation reduces the rate of recurrent mood episodes and enhances medication adherence. Add-on cognitive-behavioral therapy and family therapy can also improve adherence. (See 'Choosing adjunctive psychotherapy' below.)

However, it is reasonable to prescribe pharmacotherapy alone for maintenance treatment of bipolar disorder. Psychotherapy may not be available and some patients decline it.

CHOOSING PHARMACOTHERAPY

First-line — Maintenance pharmacotherapy usually consists of the same regimen that successfully treated the acute bipolar mood episode [17,19,26]. Studies that support this approach include the following:

- In a randomized trial of 148 acutely manic patients who initially remitted with open-label divalproex (valproate) and were then assigned to maintenance treatment with divalproex, lithium (an efficacious maintenance treatment), or placebo, time to recurrence was significantly longer with divalproex compared with lithium or placebo [27].

- In a randomized trial in which 1172 patients with a manic or depressive episode were initially stabilized with open-label quetiapine and then assigned to maintenance quetiapine, lithium, or placebo, time to recurrence was significantly longer with quetiapine compared to lithium or placebo [28].

Nevertheless, medications can be distinguished as first, second, and third-line maintenance treatments, based upon the quality and quantity of data that demonstrate the efficacy of each drug in preventing recurrent bipolar mood episodes. Medications also vary in the type, frequency, and severity of adverse effects, which influences clinician and patient preferences. As an example, a meta-analysis of six observational studies (n = 637 patients) found that the metabolic syndrome was present in more patients taking antipsychotics, compared with patients not treated with antipsychotics (45 versus 32 percent) [29].

Clinicians should initially attempt to manage patients with monotherapy to enhance compliance and minimize side effects and costs [4]. However, many patients require medication combinations for acute and maintenance treatment [13]. (See 'Patients with frequent relapses or

partial response' below and "Bipolar mania and hypomania in adults: Choosing pharmacotherapy", section on 'Severe manic episodes'.)

Second-line — For patients who do not tolerate first-line maintenance pharmacotherapy (ie, the regimen that resolved the acute bipolar mood episode), the following medications are considered second-line monotherapy because each has consistently demonstrated its efficacy in multiple randomized trials; the drugs are presented in our general order of preference based upon efficacy in reducing the risk of suicide, the number of trials conducted, risk of side effects, and cost:

- Lithium
- Valproate (divalproex)
- Quetiapine
- Lamotrigine

Use of lithium, valproate, quetiapine, or lamotrigine as maintenance treatment is consistent with multiple practice guidelines [18-20,30-33].

Although we generally use valproate as a second-line medication for maintenance treatment of bipolar disorder, we regard valproate as a third-line drug for female patients of childbearing potential. Many pregnancies are unplanned, and the drug is teratogenic and associated with cognitive impairment in the offspring [34,35]. In addition, female patients with bipolar disorder who are treated with valproate are at increased risk of polycystic ovary syndrome [36].

Lithium — Lithium has been more widely studied than any other maintenance treatment for bipolar disorder. Using lithium reduces the risk of relapse by approximately 30 percent. Evidence for the efficacy of lithium includes the following:

- A meta-analysis of five randomized trials (753 patients) that evaluated lithium for one to two years found relapses occurred in fewer patients who received lithium compared with placebo (risk ratio 0.7, 95% CI 0.5-0.9) [37]. Lithium appeared especially effective in preventing manic recurrences. However, discontinuation of treatment due to adverse events was three times greater with lithium than placebo (risk ratio 3, 95% CI 1-8).

- A subsequent two-year randomized trial (n = 768) found that time to recurrence of mania or depression were each significantly longer in patients treated with lithium than placebo [28].

- In a randomized trial of patients with first-episode mania (n = 61), who were initially stabilized with lithium plus quetiapine and then randomized to lithium or quetiapine for one year, overall psychopathology, depression, psychosis, and functioning were superior with lithium [38].

The administration and side effects of lithium are discussed separately. (See "Bipolar disorder in adults and lithium: Pharmacology, administration, and management of adverse effects".)

Reduced risk of suicide — High-quality studies that included patients with unipolar depressive disorders and patients with bipolar disorder have found that maintenance treatment with lithium reduces the risk of suicide. (See "Suicidal ideation and behavior in adults", section on 'Pharmacotherapy'.)

In addition, a meta-analysis of 31 observational studies and randomized trials compared maintenance treatment with lithium to treatment without lithium in patients with unipolar major depression, bipolar disorder, or schizoaffective disorder (n >33,000) [39]. In the subgroup of bipolar patients (14 studies), suicide attempts and completed suicides occurred less often in patients who received lithium than patients who did not (relative risk 0.2, 95% CI 0.1-0.3). This was consistent with the finding in the total sample that suicide attempts and deaths occurred in fewer patients who received maintenance lithium.

A subsequent study of self-harm used electronic health records from a nationally representative sample to identify patients with bipolar disorder (n >6000) who received maintenance monotherapy with lithium, valproate, olanzapine, or quetiapine [40]. Self-harm included any nonfatal act of self-injury, regardless of suicidal intent. Propensity scoring was used to match the patients with regard to observed potential confounders (eg, sex, comorbid disorders, and prior history of self-harm). The analyses found that time to self-harm was longer with lithium, compared with valproate (hazard ratio 1.31, 95% CI 1.01-1.70), olanzapine (hazard ratio 1.33, 95% CI 1.01-1.75), and quetiapine (hazard ratio 1.36, 95% CI 1.00-1.87). The rate of self-harm was comparable for valproate, olanzapine, or quetiapine.

Valproate — Using valproate reduces the risk of relapse by approximately 30 percent. Evidence for the efficacy of valproate as maintenance treatment includes a meta-analysis of six randomized trials (n = 876 euthymic bipolar patients) that evaluated valproate for 6 to 24 months; the primary findings were as follows [41]:

- In two trials (n = 312) that compared valproate with placebo, fewer recurrent mood episodes occurred in patients who received valproate (relative risk 0.7, 95% CI 0.5-0.9). Valproate appeared especially effective in preventing depressive recurrences. However, weight gain, tremor, and alopecia were more common with valproate than placebo, and discontinuation of treatment due to adverse effects was greater with valproate.

- Four trials (n = 618) compared valproate with lithium and found that recurrence was comparable (relative risk 1.02, 95% CI 0.87-1.20). However, discontinuation of treatment due

to intolerance or nonadherence occurred less often with valproate (relative risk 0.7, 95% CI 0.5-0.9).

The administration and side effects (table 4 and table 5) of valproate are discussed separately. (See "Bipolar mania and hypomania in adults: Choosing pharmacotherapy", section on 'Valproate or divalproex' and "Antiseizure medications: Mechanism of action, pharmacology, and adverse effects", section on 'Valproate'.)

Quetiapine — Based upon multiple randomized trials, quetiapine is a second-line maintenance treatment for bipolar disorder:

- A two-year trial randomly assigned patients (n = 1172) who were initially stabilized with open label quetiapine to quetiapine (mean dose 546 mg per day), lithium (target trough serum concentration 0.6 to 1.2 mEq/L [0.6 to 1.2 mmol/L]), or placebo [28]. Time to recurrence of mania or depression was each longer in patients who received quetiapine than placebo. In addition, time to recurrence of depression was longer with quetiapine than lithium.

- A one-year randomized trial that compared quetiapine (300 or 600 mg per day) with placebo in 584 patients found that relapse occurred in fewer patients treated with quetiapine than placebo (24 versus 40 percent) [42]. Quetiapine appeared especially effective in preventing depressive recurrences. Discontinuation of treatment due to adverse events in patients treated with quetiapine 300 mg per day, quetiapine 600 mg per day, or placebo occurred in 8, 6, and 7 percent of patients.

In addition, quetiapine plus lithium or divalproex is beneficial as maintenance treatment for bipolar disorder. (See 'Lithium or valproate plus a second-generation antipsychotic' below.)

The administration and side effects (table 6) of quetiapine are discussed separately. (See "Bipolar major depression in adults: Choosing treatment" and "Bipolar mania and hypomania in adults: Choosing pharmacotherapy", section on 'Second-generation'.)

Lamotrigine — Maintenance treatment with lamotrigine modestly reduces the risk of relapse by approximately 16 percent, compared with placebo. In addition, the efficacy of lamotrigine appears to be comparable to that for lithium; however, tolerability is better with lamotrigine than lithium.

Evidence for the efficacy of lamotrigine includes the following:

- A meta-analysis of three trials (n = 588) compared lamotrigine with placebo and found that lamotrigine was superior (risk ratio 0.84, 95% CI 0.71-0.99) [37]. Lamotrigine appeared more

effective in delaying or preventing depression than mania or mood episodes with mixed features.

- In a meta-analysis of two trials (n = 387) that compared lamotrigine with lithium, efficacy was comparable [37]. However, discontinuation of treatment due to adverse events occurred less often with lamotrigine than lithium (risk ratio 0.5, 95% CI 0.3-0.8).

- A subsequent five year, open label, randomized trial (n = 155) compared lamotrigine with lithium and found that efficacy was comparable, but that tolerability was better with lamotrigine [43].

The administration and side effects (table 4 and table 5) of lamotrigine are discussed separately. (See "Bipolar major depression in adults: Choosing treatment" and "Antiseizure medications: Mechanism of action, pharmacology, and adverse effects", section on 'Lamotrigine'.)

Third-line — Third-line maintenance monotherapy for bipolar disorder includes:

- Aripiprazole (oral or long acting injectable formulations)
- Olanzapine
- Risperidone (oral or long acting injectable formulations)

The evidence for preventing recurrent mood episodes is less extensive and consistent for aripiprazole and risperidone, compared with second-line drugs. The efficacy of olanzapine in preventing recurrence appears to be comparable to that of second-line drugs, but the tolerability of olanzapine is poorer. Use of aripiprazole, olanzapine, or risperidone as maintenance treatment is consistent with multiple practice guidelines [17,18,20,30].

Aripiprazole — One randomized trial found that oral aripiprazole (mean dose 24 mg/day) was efficacious as maintenance treatment for bipolar disorder. In the 100 week trial (n = 161 patients), there were fewer recurrences in patients treated with aripiprazole than placebo (42 versus 63 percent) [44]. Common aripiprazole side effects included tremor, akathisia, hypertension, dry mouth, weight gain, vaginitis, and flu syndrome.

Randomized trials that studied aripiprazole as adjunctive maintenance treatment have yielded inconsistent results. (See 'Patients with frequent relapses or partial response' below.)

The administration and side effects (table 6) of oral aripiprazole are discussed separately. (See "Bipolar mania and hypomania in adults: Choosing pharmacotherapy", section on 'Second-generation'.)

Long-acting injectable aripiprazole — Patients with bipolar disorder who are stabilized on daily oral aripiprazole may prefer a regimen of long-acting injectable (depot) aripiprazole once every four weeks for maintenance pharmacotherapy. However, many patients refuse depot aripiprazole because they dislike receiving injections, and most clinicians and experts do not use depot medications [45]. In addition, long-acting injectable antipsychotics do not necessarily improve adherence. (See "Bipolar disorder in adults: Managing poor adherence to maintenance pharmacotherapy", section on 'Long-acting injectable antipsychotics'.)

Evidence regarding the efficacy of long-acting injectable aripiprazole as maintenance treatment for bipolar disorder includes a 52-week randomized trial that compared long-acting injectable aripiprazole with injectable placebo in 266 patients [46]. Patients were enrolled during an episode of mania, stabilized on oral aripiprazole (15 to 30 mg/day), then stabilized on long-acting injectable aripiprazole (either 300 mg or 400 mg every month), and then randomly assigned to injectable aripiprazole or injectable placebo. Relapse of mood episodes occurred in fewer patients treated with active drug than placebo (27 versus 51 percent). Specifically, active drug was effective for preventing mania but not depression. During the stabilization phase prior to randomization, adverse events due to aripiprazole included akathisia (17 percent), weight increase (11 percent), insomnia (10 percent), and anxiety (7 percent). During the randomized phase, these four side effects occurred more often with long-acting injectable aripiprazole than placebo; nevertheless, it appeared that discontinuation of treatment due to side effects occurred less often with aripiprazole than placebo (17 versus 26 percent of patients).

Olanzapine — Although multiple studies have consistently found that olanzapine delays or prevents recurrences of bipolar disorder [47,48], we use olanzapine as a third-line maintenance treatment because it causes serious weight gain and may also cause diabetes mellitus [49-51].

Five randomized trials with different designs have studied olanzapine for maintenance treatment of bipolar disorder [47,48]. As an example, a 48-week trial compared olanzapine (mean dose 13 mg per day) with placebo in 361 patients and found that relapse occurred in fewer patients who received olanzapine than placebo (47 versus 80 percent) [52]. Olanzapine appeared to delay or prevent mania more effectively than major depression [47,48].

The administration and side effects (table 6) of olanzapine are discussed separately. (See "Bipolar mania and hypomania in adults: Choosing pharmacotherapy", section on 'Second-generation'.)

Risperidone — Risperidone may help prevent recurrence of bipolar mood episodes; when we prescribe the drug, we typically use the daily oral formulation. Although long-acting injections every two weeks are a reasonable alternative, many patients refuse depot risperidone because they dislike receiving injections, and most clinicians and experts do not use depot risperidone

[45]. In addition, long-acting injectable antipsychotics do not necessarily improve adherence. (See "Bipolar disorder in adults: Managing poor adherence to maintenance pharmacotherapy", section on 'Long-acting injectable antipsychotics'.)

No randomized trials have evaluated oral risperidone for maintenance treatment of bipolar disorder; however, randomized trials have found that long-acting injectable (depot) risperidone may be efficacious. Also, randomized trials with other second-generation antipsychotics, such as olanzapine and quetiapine, provide indirect evidence that supports using oral risperidone.

Two randomized trials have evaluated long-acting injectable (depot) risperidone as maintenance treatment for patients whose acute mania was initially stabilized with open label risperidone. Only one trial was positive:

- One two-year trial (n = 303) compared depot risperidone (generally 25 mg every two weeks) with placebo; recurrent mood episodes occurred in fewer patients who received risperidone than placebo (29 versus 52 percent) [53]. Risperidone appeared more efficacious in delaying or preventing mania than major depression.

- An 18-month trial (n = 398) compared depot risperidone (generally 25 mg every two weeks) plus oral placebo, injectable placebo plus oral placebo, and injectable placebo plus oral olanzapine (10 mg per day) [54]. Recurrence was comparable for depot risperidone plus oral placebo, compared with placebo injection plus oral placebo (39 and 56 percent of patients). By contrast, recurrent mood episodes occurred in fewer patients treated with placebo injection plus oral olanzapine, compared with placebo injection plus oral placebo (24 versus 56 percent).

A third trial found that long-acting injectable risperidone plus lithium or divalproex was beneficial as maintenance treatment for bipolar disorder. (See 'Lithium or valproate plus a second-generation antipsychotic' below.)

The administration (table 7) and side effects (table 6) of long-acting injectable risperidone are discussed separately in the context of schizophrenia. (See "Schizophrenia in adults: Pharmacotherapy with long-acting injectable antipsychotic medication".)

Other options — For the many bipolar patients who are refractory to maintenance treatment with first, second, or third-line medications, other options include asenapine, carbamazepine, lurasidone, oxcarbazepine, or paliperidone. However, the evidence supporting the use of these other options is less compelling compared with second and third-line drugs, as well as certain medication combinations. (See 'Second-line' above and 'Third-line' above and 'Patients with frequent relapses or partial response' below.)

Asenapine — A 49-week, double-blind, extension study was conducted with 218 patients who completed a three-week randomized trial that compared asenapine with olanzapine for treatment of acute manic or mixed episodes; the efficacy of asenapine and olanzapine as maintenance treatment appeared to be comparable [55]. In a subsequent study, patients with manic or mixed episodes who responded to asenapine (n = 253) were randomly assigned to maintain asenapine for 26 weeks or switch to placebo; time to recurrence of any mood episode was longer with asenapine [56].

The administration and side effects (table 6) of asenapine are discussed separately. (See "Bipolar mania and hypomania in adults: Choosing pharmacotherapy", section on 'Second-generation'.)

Carbamazepine — A meta-analysis of four randomized maintenance trials (n = 464) compared carbamazepine with lithium and found that prevention of recurrence or hospitalization was comparable; however, none of the studies included a placebo arm [57]. Many clinicians attempt to achieve a target 12-hour serum trough carbamazepine concentration of 4 to 8 mcg/mL, but there is no relationship between this blood level range and efficacy for maintenance treatment of bipolar disorder. The administration and side effects (table 4 and table 5) of carbamazepine are discussed separately. (See "Bipolar mania and hypomania in adults: Choosing pharmacotherapy", section on 'Carbamazepine' and "Antiseizure medications: Mechanism of action, pharmacology, and adverse effects", section on 'Carbamazepine'.)

Lurasidone — A maintenance trial involved 496 patients with acute bipolar mood episodes who were initially stabilized on lurasidone (20 to 80 mg/day) in combination with either lithium or valproate, and then randomized to lurasidone or placebo (plus lithium or valproate) for 28 weeks [58]. Across multiple outcome measures, time to recurrence of mood episodes was generally comparable in the two groups.

The administration and side effects (table 6) of lurasidone are discussed separately. (See "Bipolar major depression in adults: Efficacy and adverse effects of second-generation antipsychotics", section on 'Lurasidone'.)

Oxcarbazepine — A systematic review found insufficient evidence to recommend oxcarbazepine for maintenance treatment of bipolar disorder [59]. However, oxcarbazepine is an alternative to carbamazepine, based upon limited evidence of effectiveness in treating acute mood episodes and its structural similarity to carbamazepine [60-62]. In addition, oxcarbazepine is generally better tolerated and is easier to prescribe because it does not induce its own metabolism, as carbamazepine does. The administration and side effects (table 4 and table 5) of oxcarbazepine are discussed separately. (See "Antiseizure medications: Mechanism of action, pharmacology, and adverse effects", section on 'Oxcarbazepine'.)

Paliperidone — A two year randomized maintenance trial compared paliperidone extended release (median dose 6 mg per day) with placebo in 290 patients with bipolar disorder who initially remitted from acute manic or mixed episodes with paliperidone [63]. The median time to recurrence was longer in patients who received paliperidone than placebo (558 versus 283 days). The study also included 82 patients who remitted with olanzapine and were maintained on it (median dose 10 mg per day). In this non-randomized arm, time to recurrence was longer with olanzapine than in either the randomized paliperidone or placebo arms.

The administration and side effects (table 6) of paliperidone are discussed separately.

Patients with frequent relapses or partial response — Relapse frequently occurs in bipolar disorder despite maintenance monotherapy. The evidence supports using medication combinations (polypharmacy) for acute and maintenance treatment of these relapses [64]. Medication combinations are also used for patients who have a partial but inadequate response to a maintenance drug that is tolerated.

Most patients with a past history of multiple (eg, three) recurrences are treated acutely for subsequent mood episodes with a medication combination [65-67]; the combination should be continued for maintenance treatment because the increased efficacy of medication combinations often outweighs the increased side effects and costs [68]. In addition, for patients who have a partial but inadequate response to monotherapy that is tolerated, we suggest adding a second medication. Among the many possible medications combinations, we suggest lithium or divalproex plus a second-generation antipsychotic, which several trials have found is more efficacious than either lithium or divalproex monotherapy [69-73]. Lithium plus valproate, carbamazepine, or lamotrigine are reasonable alternatives.

The majority of randomized trials that have tested medication combinations have initially treated the acute mood episode with the combination. Following remission, patients were randomly assigned to maintenance treatment with the combination or monotherapy (by substituting placebo for one of the medications in the combination).

Clinicians prescribing medication combinations for maintenance therapy should try to follow certain principles [64,74]:

- Attempt to prescribe only two medications, although three may be necessary
- The combination should not pose significantly greater safety or tolerability risks than monotherapy; however, tolerability can be worse with combined treatments than monotherapy, especially if each drug is not carefully titrated to below its side effects threshold

- The combined drugs should not have the same or opposing mechanisms of action

In addition, clinicians need to be aware of possible pharmacokinetic interactions. As an example, divalproex (valproate) inhibits hepatic P450 enzymes and metabolism of concomitant medications. Conversely, carbamazepine induces hepatic enzymes and metabolism of concomitant medications. Specific drug-drug interactions can be determined using the Lexicomp drug interactions tool (Lexi-Interact Online) included in UpToDate.

Lithium or valproate plus a second-generation antipsychotic — Randomized maintenance trials for bipolar disorder have found that lithium or divalproex plus a second-generation antipsychotic is superior to lithium or valproate monotherapy [69-73]. In order of preference, we suggest adjunctive quetiapine, long-acting injectable risperidone (oral risperidone is a reasonable alternative), ziprasidone, olanzapine, or aripiprazole:

- **Quetiapine** – Two similar randomized trials that each lasted two years compared adjunctive quetiapine with placebo in patients receiving lithium or divalproex (total n = 1334) [69,70]. Relapse occurred in fewer patients treated with adjunctive quetiapine compared with placebo (19 and 20 versus 49 and 52 percent). Consistent with this finding, a pooled subgroup analysis of 445 patients who initially remitted from mood episodes with mixed features prior to maintenance treatment found that there were fewer recurrences with adjunctive quetiapine than placebo (21 versus 54 percent) [75].

- **Long-acting injectable risperidone** – In a one-year randomized trial (124 patients treated with lithium, divalproex, and/or other medications), recurrence occurred in fewer patients who received adjunctive long-acting injectable risperidone compared with placebo (23 versus 46 percent) [71].

- **Ziprasidone** – In a six-month randomized trial (240 patients treated with lithium or divalproex), the median time to a mood episode was longer in patients who received adjunctive ziprasidone compared with placebo (43 versus 27 days) [73].

- **Olanzapine** – In an 18-month randomized trial (68 asymptomatic patients treated with lithium or valproate), the median time to relapse of symptoms was longer for adjunctive olanzapine compared with placebo (163 versus 42 days) [72]. However, time to relapse of a mood syndrome (mania or depression) was comparable for the two groups, as was the number of patients with syndromic relapse.

- **Aripiprazole** – One maintenance trial of adjunctive aripiprazole found that the drug was efficacious, whereas a smaller and shorter trial did not:

- A one-year randomized trial compared adjunctive aripiprazole with placebo in 337 patients treated with lithium or valproate [76]. Recurrence occurred in fewer patients who received add-on aripiprazole than placebo (17 versus 29 percent).

- A six-month randomized trial compared aripiprazole plus divalproex with placebo plus divalproex in 83 patients, and found that there was a trend for a longer time to relapse in patients treated with adjunctive aripiprazole [77].

Additional information about lithium, divalproex, quetiapine, long-acting injectable risperidone, ziprasidone, olanzapine, and aripiprazole is discussed separately. (See 'Lithium' above and 'Valproate' above and 'Quetiapine' above and 'Risperidone' above and 'Olanzapine' above and "Second-generation antipsychotic medications: Pharmacology, administration, and side effects".)

Open-label prospective or retrospective studies suggest that clozapine added to any combination of lithium, anticonvulsants, antidepressants, or anxiolytics may delay or prevent relapse of bipolar mood episodes [78-80]. Clozapine can cause a potentially lethal agranulocytosis, and thus requires regular monitoring of white blood cell counts every one or two weeks. In addition, clozapine should not be combined with carbamazepine because they both adversely affect hematopoiesis. Additional information about the administration and side effects (table 6) of clozapine is discussed separately.

For patients who respond to maintenance treatment with an adjunctive second-generation antipsychotic, we suggest continuing the antipsychotic for a minimum of six months. Although maintaining the drug for longer (eg, two years) is reasonable, if adverse effects such as weight gain intervene after six months, it is appropriate to then taper and discontinue the antipsychotic over two to four weeks. Evidence supporting this approach includes the randomized trials described immediately above. In addition, a study enrolled patients (n = 159) who were successfully treated for mania with lithium (0.6 to 1.2 mmol/L) or valproate (350 to 830 micromol/L) plus olanzapine (5 to 25 mg/day) or risperidone (1 to 6 mg/day) [81]. After two to six weeks of remission, patients were randomly assigned to placebo substitution for the antipsychotic at randomization (monotherapy), placebo substitution for the antipsychotic at 6 months, or combination treatment for the entire 12 months of the study. Relapse occurred more often in the monotherapy group than the 6- and 12-month groups, but was comparable for the 6- and 12-month groups. The estimated rate of relapse at one year in the monotherapy, six-month, and 12-month groups was 85 versus 65 and 65 percent.

Additional information about duration of maintenance treatment is discussed elsewhere in this topic. (See 'Maintenance of medications' below.)

Lithium plus an anticonvulsant — Lithium combined with an anticonvulsant is often more effective than lithium monotherapy for maintenance treatment of bipolar disorder [82-84]:

- In a two-year, open label randomized trial (n = 220 patients), relapse occurred in fewer patients treated with lithium plus valproate than valproate monotherapy (54 versus 69 percent) [85].
- In a one-year randomized trial (n = 52 patients), lithium plus carbamazepine led to fewer mood episodes per year compared with lithium alone or carbamazepine alone (4.6 versus 6.3 and 6.7) [86].
- A randomized trial compared lamotrigine plus lithium with placebo plus lithium in 124 patients and found that the median time to relapse with adjunctive lamotrigine and placebo was 10 and 4 months [87].
- A one-year randomized trial (n = 55) compared oxcarbazepine plus lithium with placebo plus lithium and found that recurrence with adjunctive oxcarbazepine and with placebo was 38 and 59 percent [88]. Although the difference was not statistically significant, a difference of this magnitude, if real, would be clinically meaningful.

Other combinations — A one-year randomized trial (n = 351 patients) that compared aripiprazole plus lamotrigine with placebo plus lamotrigine found that the estimated rate of relapse was comparable (11 and 23 percent of patients) [89].

Potentially problematic drugs

Antidepressants — There are some concerns that maintenance treatment with antidepressants may destabilize patients with bipolar disorder. The use of antidepressants for maintenance treatment of bipolar disorder is discussed separately. (See "Bipolar major depression in adults: Efficacy and adverse effects of antidepressants".)

Benzodiazepines — Benzodiazepines during maintenance treatment may be associated with an increased risk of recurrence. An observational study from the Systematic Treatment Enhancement Program for Bipolar Disorder (STEP-BD) examined 1365 patients who recovered from a mood episode [90]. After adjusting for potential confounds, use of a benzodiazepine on a standing or as-needed basis following recovery was associated with an increased risk of recurrence (hazard ratio 1.21, 95% CI 1.01-1.45). Comparable effects were observed in additional analyses from the same study, including one that stratified the sample by propensity score (a summary measure of the likelihood of receiving a benzodiazepine). However, patients with a greater likelihood of suffering relapses may have been more likely to receive benzodiazepines.

MONITORING

We suggest regularly monitoring patients with self-report rating scales during ongoing treatment (often referred to as measurement based care). Although there is no evidence demonstrating that this practice improves outcomes, possible benefits include identifying nonresponders, detecting residual or prodromal symptoms, and helping patients recognize the degree of improvement or lack thereof. In addition, patients may become more engaged in treatment as they take an active role, and may be able to relate specific behaviors with symptomatic changes.

Measurement based care can be implemented with self-report measures that are in the public domain (free), require little additional time on the part of the clinician, and approximately 5 to 10 minutes for patients to complete while waiting for their appointments [91]. Reasonable options in order of preference include the following:

- The Life Chart Method (figure 1), with which patients rate their overall mood on a daily basis; the rating is completed at the end of each day. A prospective study found preliminary evidence of good validity for patient self-reports [92]. Prior studies have established the reliability and validity of clinician ratings using the instrument [93,94]. In addition, a manual that provides standardized instructions for patients is available.

- The first 13 items of the Mood Disorder Questionnaire (table 8) to track symptoms of mania/hypomania (validity has been established for clinician ratings but not for patient self-reports) [95], as well as the nine-item Patient Health Questionnaire (table 9) to track symptoms of depression (this instrument is well established for patients with unipolar depression) [96]. Patients can complete these instruments in approximately 5 to 10 minutes while waiting for their appointments [91].

- A single Likert response item (form 1) that assesses mood on a daily basis, and is anchored on one end with 0 for very sad, 10 on the other end for very happy, and 5 in the middle for normal mood (euthymia).

Other alternatives include the Internal State Scale [97] as well as instruments that can be downloaded from the Depression and Bipolar Support Alliance website. In addition, My Mood Monitor is a 27-item instrument that is used to screen for multiple psychiatric disorders including bipolar disorder; the instrument can be downloaded from the journal website for longitudinal monitoring [98].

Additional information about measurement based care, including the Patient Health Questionnaire, is discussed separately in the context of depression. (See "Using scales to monitor

symptoms and treat depression (measurement based care)".)

MAINTENANCE OF MEDICATIONS

Duration — The duration of maintenance treatment will vary for each patient. Most patients require maintenance treatment for many years, and some patients require it their entire lives because medications are not curative [99]. Maintenance treatment should last longer for patients with a more severe course of illness. Factors to consider include the following:

- Number of years the patient has had bipolar disorder
- Lifetime number of mood episodes and hospitalizations, the length of time required to stabilize the patient after each episode, and how many years have elapsed since the last episode
- Lifetime number of suicide attempts and their lethality

Discontinuation — Most patients require maintenance treatment for many years, and some patients require it for their entire lives. However, patients may want to stop maintenance medications because of side effects, inadequate response, medical illness, pregnancy, or a wish to be medication-free after a prolonged period of euthymia.

Discontinuing lithium — Discontinuing stable treatment usually leads to a new mood episode:

- In a review of 14 lithium maintenance treatment studies that involved discontinuation of lithium in 257 patients who had previously been stable for a mean of 30 months, more than 50 percent of the patients suffered a recurrence within 10 weeks of discontinuing lithium, and about 90 percent relapsed within the first year off of treatment [100].
- In a subsequent study, among 32 patients successfully treated with maintenance lithium for a minimum of five years, 32 percent suffered a recurrence within one month of discontinuing lithium, and 62 percent within one year [101].

Other risks of stopping maintenance treatment include hospitalization, persistent subsyndromal symptoms, family and economic losses, and suicide. Psychoeducation may help discourage patients from discontinuing effective maintenance treatment. (See "Bipolar disorder in adults: Managing poor adherence to maintenance pharmacotherapy", section on 'Consequences' and "Bipolar disorder in adults: Psychoeducation and other adjunctive maintenance psychotherapies", section on 'Group psychoeducation'.)

If patients insist on stopping treatment, we suggest slowly tapering one medication at a time, over a period of several weeks to months. Clinicians should also monitor patients frequently for prodromal symptoms of early recurrence. Prospective, open-label studies show that tapering maintenance medication more slowly is associated with lower rates of recurrence, but that most patients suffer a recurrence despite the slower taper:

- In 78 patients who were effectively maintained on lithium for a mean of four years and then discontinued it, recurrence within two years was significantly greater in patients who stopped lithium in less than two weeks compared with discontinuation over two to four weeks (95 versus 69 percent) [102].

- In 64 patients who were stable on maintenance lithium for a mean of four years and then discontinued it, recurrence within five years was significantly greater in patients who stopped lithium in less than two weeks compared with discontinuation over two to four weeks (94 versus 53 percent) [103].

Discontinuing antipsychotic — Maintenance of antipsychotic treatment appears to lower the risk of recurrence of symptoms in individuals who are stabilized on medications. As an example, in a meta-analysis of eight studies and over 2900 subjects, individuals with bipolar I disorder (stabilized on mood stabilizer plus second-generation antipsychotic) were maintained on either mood stabilizer plus second-generation antipsychotic (n = 1456) versus mood stabilizer plus placebo (n = 1476) [104]. At six months, individuals in the treatment group (second-generation antipsychotic plus mood stabilizer) exhibited a lower recurrence than the control group (mood stabilizer plus placebo) of any mood episode (relative risk 0.51, 95% CI 0.39-0.86), manic/hypomanic or mixed episode (relative risk 0.42, 95% CI 0.3-0.59), and depressive episode (relative risk 0.39, 95% CI 0.28-0.54). Additionally, the secondary outcome (recurrence at 12 months) showed similar lower recurrence rates for the second-generation antipsychotic plus mood stabilizer group versus mood stabilizer plus placebo group for each type of recurrence.

Patient considerations — Some patients are discouraged by the prospect of taking medications "forever" [4]. Female patients may interrupt maintenance treatment in order to conceive children, others may have intolerable side effects that may truncate maintenance treatment. We educate patients about the course of illness in bipolar disorder and the potential benefits of ongoing treatment. Additionally, we emphasize that in the context of the long-term relationship with the patient the need for maintenance treatment will periodically be re-evaluated based on their progress in maintaining symptomatic and functional stability. It may also help to point out that other chronic illnesses such as hypertension, diabetes mellitus, and asthma often require lifetime medications. Additional information about adherence with maintenance medications for

bipolar disorder is discussed separately. (See "Bipolar disorder in adults: Managing poor adherence to maintenance pharmacotherapy".)

Based upon clinical experience, discontinuation of maintenance pharmacotherapy may be more successful for patients who have established relationships with their clinicians, as well as patients who have relatively few current psychosocial stressors such as relationship or occupational difficulties, getting married, or graduating from school. We typically educate patients about relapse prevention (eg, identifying prodromal symptoms and avoiding risk factors for relapse such as substance abuse), and assist in developing a plan for patients and families to follow should relapse occur.

CHOOSING ADJUNCTIVE PSYCHOTHERAPY

Although pharmacotherapy is the cornerstone of maintenance treatment for bipolar disorder, adjunctive psychotherapy can help prevent relapses and improve medication adherence. As an example, a meta-analysis of eight randomized trials (n = 830 patients) compared psychotherapy (eg, group psychoeducation, cognitive-behavioral therapy, or family therapy) plus pharmacotherapy with pharmacotherapy alone; the probability of relapse was lower in patients treated with adjunctive psychotherapy (odds ratio 0.5, 95% CI 0.4-0.7) [105]. Adjunctive psychotherapy is typically administered during maintenance treatment to euthymic patients, who are typically better able to participate in psychotherapy than acutely ill patients [106].

However, if adjunctive psychotherapy is used during an acute mood episode, the same psychotherapy is usually retained for maintenance treatment. This practice is supported by a randomized trial of 82 patients with acute mood episodes who were stabilized for four weeks with pharmacotherapy plus one of two randomly assigned adjunctive psychotherapies (either interpersonal and social rhythm therapy or the control therapy, called intensive clinical management) [107]. Following stabilization, patients were randomly assigned again to maintenance treatment with the same psychotherapy or to switch to the other psychotherapy. Relapse occurred in fewer patients who maintained the same therapy compared with those who switched (18 versus 40 percent).

Choosing a specific adjunctive psychotherapy is based upon the quality and quantity of data that demonstrate its efficacy in preventing recurrent bipolar mood episodes, as well as its beneficial effects upon medication adherence.

First-line — For bipolar patients receiving maintenance pharmacotherapy, we suggest adjunctive group psychoeducation as first-line psychotherapy. Psychoeducation is a structured, time-limited program that teaches patients and family members about bipolar disorder, including its

pathogenesis, clinical features, course of illness, and treatment; the program also addresses detecting prodromal symptoms. Nearly all other types of psychotherapy used for bipolar disorder include an element of psychoeducation because of its demonstrated success and the ease of administration. Several randomized trials indicate that group psychoeducation is efficacious both for preventing recurrent mood episodes and improving adherence to pharmacotherapy. The efficacy, administration, and content of group psychoeducation are discussed separately. (See "Bipolar disorder in adults: Psychoeducation and other adjunctive maintenance psychotherapies", section on 'Group psychoeducation' and "Bipolar disorder in adults: Managing poor adherence to maintenance pharmacotherapy", section on 'Group psychoeducation'.)

Second-line — Bipolar patients receiving maintenance pharmacotherapy may decline or not have access to group psychoeducation, or may continue to demonstrate poor adherence despite treatment with group psychoeducation. For these patients, we suggest either adjunctive cognitive-behavioral therapy (CBT) or family therapy for enhancing poor medication adherence. Multiple randomized trials indicate that CBT and family therapy are each efficacious for improving adherence. (See "Bipolar disorder in adults: Managing poor adherence to maintenance pharmacotherapy", section on 'Specific interventions'.)

The efficacy of CBT and of family therapy for delaying or preventing recurrent bipolar mood episodes is not clear, due to inconsistent results across different randomized trials. (See "Bipolar disorder in adults: Psychoeducation and other adjunctive maintenance psychotherapies".)

ELECTROCONVULSIVE THERAPY

Maintenance electroconvulsive therapy (ECT) has been used for patients who respond to ECT for treatment of acute mood episodes and subsequently fail many other maintenance medication regimens and psychotherapies [18]. Most of the evidence supporting the effectiveness and tolerability of maintenance ECT comes from small observational studies [108-116]. In one three-year retrospective study including 43 individuals with bipolar disorder, the number of psychiatric hospitalizations and the mean annual number of days hospitalized were lower during maintenance ECT compared with the time period before initiation of maintenance ECT (number of psychiatric hospitalizations: 8 versus 32; relative risk 0.24, 95% CI 0.13-0.43; number of days hospitalized: 115 versus 826; relative risk 0.14, 95% CI 0.07-0.29, respectively) [117]. Of the 37 individuals who were hospitalized before maintenance ECT, only 14 of them were hospitalized during the course of maintenance ECT (ie, 62 percent reduction in hospitalization). Furthermore, only individuals who were hospitalized prior to maintenance ECT were hospitalized during the maintenance treatment.

Maintenance medications, including anticonvulsants, are often prescribed in conjunction with maintenance ECT.

Additional information about using ECT for bipolar disorder, as well as an overview of ECT and the technique for performing ECT, are discussed separately. (See "Bipolar disorder in adults: Indications for and efficacy of electroconvulsive therapy" and "Overview of electroconvulsive therapy (ECT) for adults" and "Technique for performing electroconvulsive therapy (ECT) in adults".)

SELF-MANAGEMENT

Patients who can take responsibility for their health may perhaps benefit from self-management strategies that include measures to [118]:

- Calm oneself and cope with stress (eg, scheduling relaxing activities or learning mindfulness-based stress reduction).
- Optimize medical management by adhering to treatment and recognizing prodromal signs. Regular mood charting (figure 1) may be helpful. (See 'Monitoring' above.)
- Maintain hope, for example, understanding that bipolar disorder is a medical disorder that can be treated and if current treatment is not working sufficiently, there are many other alternatives.
- Engage in physical activity and exercise (eg, bicycle riding or walking).
- Maintain a healthy diet.

However, some self-management interventions may not prevent relapses of mood episodes. As an example, a 16-week randomized trial compared usual care plus a smartphone application with usual care alone in 205 patients with bipolar I disorder who did not have a current mood episode [119]. The self-management intervention consisted of a smartphone application and nonclinician coaches, and included self-assessment of medication adherence and wellness, and prompts to contact clinicians when indicated. At the week 48 follow-up assessment, time to recurrence of bipolar mood episodes in the two groups was comparable.

GERIATRIC PATIENTS

Maintenance treatment for geriatric bipolar disorder is discussed separately. (See "Geriatric bipolar disorder: Maintenance treatment".)

FEMALE PATIENTS

For female patients who are at high risk of unintended pregnancies (eg, become hypersexual when manic or have a history of irregular use of contraceptives), we try to avoid using teratogenic drugs, especially valproate, but also carbamazepine and lithium. The teratogenic and postnatal risks caused by these drugs are discussed separately. (See "Teratogenicity, pregnancy complications, and postnatal risks of antipsychotics, benzodiazepines, lithium, and electroconvulsive therapy" and "Risks associated with epilepsy during pregnancy and the postpartum period", section on 'Effects of ASMs on the fetus and child'.)

Pregnancy — Preconception and prenatal maintenance pharmacotherapy for bipolar patients, and contraception and preconception counseling for bipolar disorder are discussed separately. (See "Bipolar disorder in women: Preconception and prenatal maintenance pharmacotherapy" and "Bipolar disorder in women: Indications for preconception and prenatal maintenance pharmacotherapy" and "Bipolar disorder in women: Contraception and preconception assessment and counseling".)

SOCIETY GUIDELINE LINKS

Links to society and government-sponsored guidelines from selected countries and regions around the world are provided separately. (See "Society guideline links: Bipolar disorder".)

INFORMATION FOR PATIENTS

UpToDate offers two types of patient education materials, “The Basics” and “Beyond the Basics.” The Basics patient education pieces are written in plain language, at the 5th to 6th grade reading level, and they answer the four or five key questions a patient might have about a given condition. These articles are best for patients who want a general overview and who prefer short, easy-to-read materials. Beyond the Basics patient education pieces are longer, more sophisticated, and more detailed. These articles are written at the 10th to 12th grade reading level and are best for patients who want in-depth information and are comfortable with some medical jargon.

Here are the patient education articles that are relevant to this topic. We encourage you to print or e-mail these topics to your patients. (You can also locate patient education articles on a variety of subjects by searching on “patient info” and the keyword(s) of interest.)

- Basics topics (See "Patient education: Bipolar disorder (The Basics)" and "Patient education: Coping with high drug prices (The Basics)".)

- Beyond the Basics topics (See "Patient education: Bipolar disorder (Beyond the Basics)" and "Patient education: Coping with high prescription drug prices in the United States (Beyond the Basics)".)

These educational materials can be used as part of psychoeducational psychotherapy. (See 'First-line' above.)

The National Institute of Mental Health also has educational material explaining the symptoms, course of illness, and treatment of bipolar disorder in a booklet entitled "Bipolar Disorder," which is available online at the website or through a toll-free number, 866-615-6464. The web site also provides references, summaries of study results in language intended for the lay public, and information about clinical trials currently recruiting patients.

More comprehensive information is provided in many books written for patients and family members, including The Bipolar Disorder Survival Guide: What You and Your Family Need to Know, written by David J. Miklowitz, PhD (published by The Guilford Press, 2002); An Unquiet Mind: A Memoir of Moods and Madness, written by Kay Jamison, PhD (published by Random House, 1995); and Treatment of Bipolar Illness: A Casebook for Clinicians and Patients, by RM Post, MD, and GS Leverich, LCSW (published by Norton Press, 2008).

The Depression and Bipolar Support Alliance (800-826-3632) is a national organization that educates members about bipolar disorder and how to cope with it. Other functions include increasing public awareness of the illness and advocating for more research and services. The organization is administered and maintained by patients and family members, and has local chapters.

The National Alliance on Mental Illness (800-950-6264) is a similarly structured organization devoted to education, support, and advocacy for patients with any mental illness. Bipolar disorder is one of their priorities.

SUMMARY AND RECOMMENDATIONS

- **Indications** – Bipolar disorder is a highly recurrent illness. For euthymic patients with bipolar I disorder, we recommend maintenance pharmacotherapy rather than no treatment (**Grade 1A**). We also suggest maintenance treatment for patients with bipolar II disorder rather than no treatment (**Grade 2C**). Patients with other specified bipolar disorder are likely to benefit from maintenance treatment as well. (See 'Indications' above.)

- **First-line treatment** – For most patients who respond to acute pharmacotherapy, we suggest maintenance treatment with the same regimen, rather than switching medications (**Grade 2B**). (See 'First-line' above.)

- **Second- and third-line treatment** – For patients who do not tolerate the initial course of maintenance pharmacotherapy and were not treated with lithium, we suggest lithium monotherapy over other medication regimens (**Grade 2B**).

  For patients who do not respond to or tolerate lithium, we suggest valproate, quetiapine, or lamotrigine rather than other medications (**Grade 2B**). For patients who do not respond to or cannot tolerate these drugs, aripiprazole, olanzapine, or risperidone are reasonable alternatives. (See 'Second-line' above and 'Third-line' above.)

- **Patients with frequent relapses or partial response** – For patients who have a history of multiple recurrences or have a partial but inadequate response to a maintenance drug that is tolerated, we suggest adding a second medication (**Grade 2B**). Common combinations include lithium or valproate, plus a second-generation antipsychotic, such as quetiapine, long-acting injectable risperidone, ziprasidone, or olanzapine. Other combinations that are useful include lithium plus valproate or carbamazepine. (See 'Patients with frequent relapses or partial response' above.)

- **Adjunctive psychotherapy** – For patients with bipolar disorder, we suggest adjunctive psychoeducation for euthymic patients rather than no psychotherapy (**Grade 2C**). Group psychoeducation as adjunctive treatment with pharmacotherapy can prevent recurrent mood episodes and enhance medication adherence. Adjunctive cognitive-behavioral therapy or family therapy are each a reasonable alternative to psychoeducation for management of poor adherence to pharmacotherapy. (See 'Choosing adjunctive psychotherapy' above.)

- **Monitoring** – Monitoring bipolar patients with rating scales during ongoing treatment may identify nonresponders, detect residual symptoms, and help patients recognize improvement. Clinicians can track symptoms of mania/hypomania with the first 13 items of the Mood Disorder Questionnaire (table 8), and symptoms of depression with the nine-item Patient Health Questionnaire (table 9). (See 'Monitoring' above.)

- **Duration of treatment** – Most patients require maintenance treatment for many years, and some patients require it their entire lives. (See 'Duration' above.)

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