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Bipolar mania and hypomania in adults: Choosing pharmacotherapy

AUTHOR: Jeffrey Stovall, MD
SECTION EDITOR: Paul Keck, MD
DEPUTY EDITOR: David Solomon, MD

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INTRODUCTION

Bipolar disorder is marked by episodes of mania (table 1) and hypomania (table 2), and nearly always includes episodes of major depression (table 3) [1]. Despite clinical differences between manic and hypomanic episodes, they are treated with the same medications [2-9].

This topic reviews choosing pharmacotherapy for acute mania and hypomania in adults. The general principles of administering pharmacotherapy for acute mania and hypomania in adults are discussed separately, as are pharmacotherapy for acute bipolar depression and maintenance treatment. (See "Acute bipolar mania and hypomania in adults: General principles of pharmacotherapy" and "Bipolar major depression in adults: Choosing treatment" and "Bipolar disorder in adults: Choosing maintenance treatment".)

DEFINITION OF BIPOLAR DISORDER

Bipolar disorder 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. Episodes of mania, hypomania, and major depression can be accompanied by symptoms of the

opposite polarity and are referred to as mood episodes with mixed features (eg, mania with mixed features). 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'.)

Despite clinical differences among manic and hypomanic episodes (eg, hypomania is less severe than mania), they are treated with the same medications [2-9].

Pharmacotherapy for manic episodes depends upon their severity. Although there are no established criteria that demarcate severe episodes from mild to moderate illness, we classify episodes as severe if they include any of the following:

- Suicidal ideation or behavior
- Homicidal ideation or behavior
- Aggressive behavior
- Psychotic features (ie, delusions or hallucinations)
- Poor judgment that places the patient or others at imminent risk of being harmed

GENERAL TREATMENT PRINCIPLES

The general principles and issues that are involved in treating acute bipolar mania and hypomania include the following:

- Nature of the evidence
- Similar approach for mania and hypomania
- Assessment and monitoring
- Level of care
- Goals
- Drug classes
- Duration of an adequate trial
- Predictors of response
- Relapse during maintenance treatment
- Destabilizing drugs
- Indications for referral

These general principles are discussed in detail separately. (See "Acute bipolar mania and hypomania in adults: General principles of pharmacotherapy".)

SEVERE MANIC EPISODES

Severe episodes of mania or mania with mixed features are medical emergencies that are characterized by suicidal or homicidal ideation or behavior, aggressiveness, psychotic features (eg, delusions or hallucinations), and/or poor judgment that places the patient or others at imminent risk of being harmed [9,10]. Severely ill patients generally require hospitalization.

Approach to treatment — We suggest that acute treatment of severe mania proceed according to the sequence depicted in the algorithm (algorithm 1) and described in the sections below. Patients begin with initial treatment and progress through each step until they respond. The duration of an adequate treatment trial is discussed separately. (See "Acute bipolar mania and hypomania in adults: General principles of pharmacotherapy", section on 'Duration of an adequate trial'.)

Initial treatment — For patients with severe mania, we suggest initial treatment with lithium plus an antipsychotic; however, valproate plus an antipsychotic is a reasonable alternative (algorithm 1). We generally combine lithium or valproate with aripiprazole, haloperidol, olanzapine, quetiapine, or risperidone. Other antipsychotics that are used less frequently include asenapine, cariprazine, or paliperidone, as well as a first-generation antipsychotic other than haloperidol. Prescribing medication combinations for severe mania is consistent with multiple treatment guidelines [2,6-9,11,12].

No head-to-head trials have compared lithium plus an antipsychotic with valproate plus an antipsychotic. Thus, the choice between lithium and valproate, and the choice of a specific antipsychotic is based upon other factors, including the patient's past response to medications, the past response of family members with bipolar disorder to medications, specific manic symptoms, side effect profiles, comorbid general medical illnesses, potential for drug-drug interactions, availability of specific drug preparations (eg, intramuscular or oral disintegrating), patient preference, and cost [6-8]. As an example, patients with:

- Renal disease generally avoid lithium
- Liver disease generally avoid valproate
- Sensitivity to extrapyramidal symptoms generally avoid aripiprazole and risperidone
- Obesity generally avoid olanzapine, quetiapine, and risperidone

In addition, women of childbearing age generally avoid valproate.

Medication side effects are discussed in more detail separately.

- (See 'Medication doses and side effects' below.)
- (See "Bipolar disorder in adults and lithium: Pharmacology, administration, and management of adverse effects", section on 'Managing lithium adverse effects'.)
- (See "Antiseizure medications: Mechanism of action, pharmacology, and adverse effects".)
- (See "First-generation antipsychotic medications: Pharmacology, administration, and comparative side effects".)
- (See "Second-generation antipsychotic medications: Pharmacology, administration, and side effects".)

Based upon several meta-analyses of randomized trials in patients with severe mania, the combination of lithium or valproate plus an antipsychotic is more efficacious than monotherapy [13-15]. As an example, a systematic review identified 19 trials that compared combination therapy with monotherapy in a total of 4250 patients with pure mania or mania with mixed features; most of the trials included patients with psychotic features who were hospitalized [16]. Combination therapy primarily consisted of lithium or valproate plus an antipsychotic; three studies included patients who received carbamazepine plus an antipsychotic. The antipsychotics consisted of aripiprazole, asenapine, haloperidol, olanzapine, paliperidone, quetiapine, risperidone, and ziprasidone. In the meta-analyses that were conducted:

- Improvement of mania was greater with combination therapy than monotherapy with lithium, valproate, or carbamazepine. However, the clinical advantage of combination therapy over monotherapy was small and heterogeneity across studies was moderate. Although discontinuation of treatment due to adverse effects was comparable for the two groups, somnolence occurred in more than twice as many patients who received combination therapy than monotherapy, and weight gain was increased by nearly a factor of four with combination therapy.

- Improvement of mania was greater with combination therapy than monotherapy with antipsychotics, the clinical benefit was small to moderate, there was no heterogeneity across studies, and discontinuation of treatment due to adverse effects was comparable for the two groups.

We generally avoid combining carbamazepine with an antipsychotic, based upon randomized trials that found this combination is no more efficacious than carbamazepine alone [17,18]. Carbamazepine induces hepatic enzymes that metabolize antipsychotics, and in one trial lowered the antipsychotic blood level by 40 percent [18]. Specific medication interactions that can occur may be determined using the Lexicomp drug interactions tool (Lexi-Interact Online) included in UpToDate.

In addition, two randomized trials indicate that adding ziprasidone to lithium or divalproex is not efficacious [13,19]. As an example, a three-week trial assigned 656 patients with pure mania or mania with mixed features who had not responded to either lithium or divalproex to receive adjunctive treatment twice per day with ziprasidone 20 to 40 mg, ziprasidone 60 to 80 mg, or placebo [19]. Neither high-dose nor low-dose ziprasidone provided any benefit.

When prescribing a medication combination, both drugs are started and titrated up simultaneously. The doses and side effects of lithium, valproate, and antipsychotics are discussed elsewhere in this topic. (See 'Medication doses and side effects' below.)

Patients who cannot tolerate combination pharmacotherapy are treated with monotherapy. (See 'First-line monotherapy' below.)

Treatment-resistant patients — A severe manic episode that does not respond to one medication combination should be treated with a second medication combination (algorithm 1). Generally, lithium is switched to valproate or vice versa. As an example, for patients who do not respond to initial treatment with lithium plus haloperidol within two weeks of reaching target doses, we suggest tapering and discontinuing lithium at the same time that valproate is started and titrated up. Lithium is generally tapered over one week by the same amount for each dose decrease (eg, lithium 1800 mg per day is decreased by 600 mg per day, every one to two days). The dose and side effects of lithium and valproate are discussed separately. (See 'Lithium' below and 'Anticonvulsants' below.)

Conversely, for patients who do not respond to initial treatment with valproate plus haloperidol within two weeks of reaching target doses, we suggest tapering and discontinuing valproate at the same time that lithium is started and titrated up. Valproate is generally tapered over one week by the same amount for each dose decrease (eg, valproate 2000 mg per day is decreased by 500 mg per day, every one to two days).

For patients who do not respond to lithium plus an antipsychotic, as well as valproate plus the same antipsychotic, we suggest starting a third medication combination involving lithium or valproate plus an antipsychotic. The choice between lithium and valproate is based upon efficacy and tolerability in the two prior trials. In addition, the antipsychotic used in the two prior trials is discontinued and a new one chosen from among aripiprazole, haloperidol (or another first-generation antipsychotic), olanzapine, quetiapine, or risperidone.

The antipsychotic is generally tapered over one week by the same amount for each dose decrease (eg, haloperidol 10 mg per day is decreased by 5 mg per day, every one to two days), and at the same time, the other antipsychotic is started and titrated up. The dose and side effects of antipsychotics are discussed separately. (See 'Antipsychotics' below.)

Treatment-refractory patients — We suggest electroconvulsive therapy (ECT) for refractory patients whose manic episode does not respond to four to six medication combinations [2,20,21]. Using ECT for mania that does not respond to pharmacotherapy is consistent with practice guidelines [6-9,12].

ECT is generally safe and there are no absolute contraindications, even in patients whose general medical status is compromised [22]. Nevertheless, safety concerns regarding ECT necessitate preprocedure medical consultation. Potential adverse effects include cardiopulmonary events, aspiration pneumonia, fractures, dental and tongue injuries, headache, nausea, and cognitive impairment. Adverse effects of ECT and medical consultation prior to ECT are discussed separately. (See "Overview of electroconvulsive therapy (ECT) for adults", section on 'Adverse effects' and "Medical evaluation for electroconvulsive therapy".)

Electrode placement and other aspects of ECT technique for treating mania have not been standardized. Thus, ECT is typically administered with the same technique used for other indications and is generally given three times per week on alternating days. Most patients, regardless of indication, remit with 6 to 12 treatments, but some patients may require 20 or more. Additional information about ECT is discussed separately. (See "Overview of electroconvulsive therapy (ECT) for adults" and "Technique for performing electroconvulsive therapy (ECT) in adults".)

Several studies suggest that ECT is effective for mania. (See "Bipolar disorder in adults: Indications for and efficacy of electroconvulsive therapy", section on 'Mania'.)

Other options

- **Clozapine** – For patients with refractory mania who decline ECT, do not remit with it, or have no access to it, and who do not respond to medication combinations involving lithium or valproate plus aripiprazole, haloperidol (or another first-generation antipsychotic), olanzapine, quetiapine, risperidone, or ziprasidone, we suggest pharmacotherapy with clozapine, either as monotherapy or combined with lithium or valproate. Using clozapine for mania that does not respond to other medications is consistent with multiple practice guidelines [6,7,9,12].

  The standard schedule for administering clozapine is to start treatment at a dose of 12.5 or 25 mg at bedtime, and then increase the dose by 25 mg per day every two days as tolerated, to a target dose of 150 to 450 mg two times per day. Although one retrospective study in patients with refractory manic or mixed episodes (n = 67) concluded that more rapid titration was safe and associated with shorter hospital stays, we generally use the standard schedule for prescribing clozapine as part of routine clinical care.

Clozapine can cause agranulocytosis and other blood dyscrasias, and clinicians must monitor complete blood counts every one or two weeks. Clozapine is also associated with the metabolic syndrome. Thus, patients taking clozapine should be regularly monitored for weight, waist circumference, blood pressure, and serum glucose and lipids. Additional information about administering clozapine and its side effects is discussed separately. (See "Second-generation antipsychotic medications: Pharmacology, administration, and side effects" and "Schizophrenia in adults: Guidelines for prescribing clozapine".)

Low-quality evidence suggests that clozapine may ameliorate refractory mania. One review identified 10 prospective observational studies, 3 retrospective studies, and 2 randomized trials; the total sample included more than 1000 patients who were manic, depressed, rapid cycling, and/or psychotic [23]. Clozapine was used as add-on therapy or as monotherapy. Across the studies, the results suggested that clozapine was beneficial and relatively well tolerated. Serious adverse effects included leukopenia (1.7 percent of patients), agranulocytosis (0.3 percent), and seizures (0.5 percent). The most common side effects were sedation (12 percent), sialorrhea (5 percent), constipation (5 percent), and weight gain (4 percent).

- **Treatments with potential benefit** – Patients unresponsive to lithium or valproate plus clozapine may possibly benefit from allopurinol plus lithium, tamoxifen monotherapy or tamoxifen plus lithium, and wearing glasses that block blue wavelength light. No head-to-head trials have compared these other treatment options. Thus, the choice is based upon other factors, including past response to medications, side effect profiles, comorbid general medical conditions, potential for drug-drug interactions, patient preference, and cost.

  - **Allopurinol** – Allopurinol, which is typically used to prevent attacks of gouty arthritis and nephropathy, appears to be beneficial as add-on treatment for acute mania, based upon meta-analyses of small randomized trials [24,25]. As an example, a meta-analysis of five inpatient and outpatient trials lasting four to eight weeks compared adjunctive allopurinol (300 or 600 mg/day) with placebo in patients with pure mania or mania with mixed features (n = 433); the patients had not responded to initial treatment with antipsychotics, lithium, and/or valproate [26]. Improvement was greater with add-on allopurinol and the clinical benefit was small to moderate; in addition, adverse effects were comparable with active drug and placebo.

  - **Tamoxifen** – Tamoxifen is a centrally active protein kinase C inhibitor that may be beneficial for refractory mania, either as monotherapy or combined with lithium or valproate. However, the drug is widely used to prevent breast cancer because it is a

selective estrogen receptor antagonist, and these antiestrogen effects preclude its use beyond patients with severe mania who are unresponsive to most or all other treatments. This approach is consistent with multiple practice guidelines [6,8,9].

Evidence supporting the use of tamoxifen for mania includes several small randomized trials [27-29]. The largest trial compared tamoxifen (20 to 40 mg two times per day) with placebo for three weeks in 66 patients hospitalized with pure mania or mania with mixed features [30]. Response (reduction of baseline symptoms ≥50 percent) occurred in more patients who received tamoxifen than placebo (48 versus 5 percent).

- **Blue-blocking glasses** – Wearing orange tinted glasses that block the blue light spectrum, which may be akin to dark therapy, may help improve manic symptoms. A small, open-label, one-week randomized trial compared add-on blue-blocking glasses with clear lens glasses in patients hospitalized with acute mania (n = 23) [31]. The glasses were worn each day from 6 p.m. to 8 AM, and patients received pharmacotherapy that included antipsychotics, lithium, and valproate. Improvement was greater with blue-blocking glasses than clear lens glasses, and the clinical effect was large despite the use of less intense pharmacotherapy for the group wearing blue-blocking glasses. Adverse effects of the blue-blocking glasses included emerging depressive symptoms in two patients, which remitted by decreasing use of the glasses.

Treatments with little to no benefit — There is little or no evidence to support treating acute mania with anticonvulsants other than valproate and carbamazepine. Based upon randomized trials, lamotrigine, gabapentin, topiramate, and zonisamide are not effective for treating mania [6,32-36]. In addition, a systematic review found that there were no randomized trials involving tiagabine, and results from observational studies were conflicting [37].

Nor do we suggest using oxcarbazepine, which has been substituted for carbamazepine to treat mania because their molecular structures are similar and oxcarbazepine has fewer side effects. There is no high quality evidence that oxcarbazepine has any benefit in adults [34,38]. In addition, a randomized trial found that oxcarbazepine and placebo were comparable in 116 children and adolescents with pure mania or mania with mixed features [39].

The calcium channel blocker verapamil has also not demonstrated efficacy for mania [34]. A meta-analysis of two randomized trials compared verapamil (480 mg/day in divided doses) with placebo in patients with acute mania (total n = 46) and found that improvement was comparable for the two groups [40].

Agitation — Agitation is defined as nonproductive, excess motor activity in conjunction with inner tension [1,41], and is common in severe mania, especially mania with mixed features [6].

The initial assessment of agitation in patients with a known diagnosis of bipolar disorder should focus upon determining whether the agitation is due to causes beyond mania, such as a general medical disorder, or intoxication or withdrawal from alcohol or other substances such as cocaine or methamphetamines [42]. In addition, clinicians should assess safety, including risk for suicide, and develop a treatment plan.

Hospitalized patients with mania who are acutely agitated often require oral, inhaled, or intramuscular medications to manage threatening or aggressive behavior, and may also require seclusion and physical restraints [6,7,9]. Oral or inhaled formulations are used for mild to moderate agitation, and intramuscular formulations for severe agitation. Patients with severe mania generally receive antipsychotics (eg, aripiprazole, haloperidol, or olanzapine) as part of their daily medication regimen (see 'Initial treatment' above), and the same antipsychotic is typically used on an as needed basis for controlling acute behavioral disturbances.

Multiple studies support treating severe manic agitation with a short-acting, intramuscular injection of a first- or second-generation antipsychotic. As an example, a randomized trial found that among psychiatric inpatients with various diagnoses who received haloperidol for acute agitation (n = 110), the median time to sedation was 20 minutes, and sedation within 120 minutes occurred in 92 percent [43]. Other studies have found that intramuscular aripiprazole, olanzapine, and ziprasidone can also be efficacious [6,44,45]. In addition, patients not responding to initial monotherapy can be treated with the combination of an antipsychotic and benzodiazepine, such as haloperidol plus lorazepam or midazolam [45].

Agitation can also be managed with benzodiazepine monotherapy [6,7,9]. As an example, agitation may be secondary to akathisia that is caused by an antipsychotic, particularly a first-generation drug such as haloperidol; in these cases, agitation can be treated with a benzodiazepine such as lorazepam, using a dose of 0.5 to 2 mg.

For mild to moderate agitation in patients who cannot tolerate as needed antipsychotics or benzodiazepines, another option is dexmedetomidine. Evidence supporting its use includes a randomized trial that enrolled 378 patients with bipolar disorder and mild to moderate agitation; nearly 80 percent were treated with daily medications for bipolar disorder. Patients were randomly assigned to receive a single dose of dexmedetomidine 180 mcg, dexmedetomidine 120 mcg, or placebo, which was self-administered as a sublingual dissolving film [46]. Improvement of agitation was greater with dexmedetomidine 180 mcg or 120 mcg than placebo, beginning 20 minutes after taking the study drug and continuing for two hours. The efficacy of the two dexmedetomidine doses was comparable. However, the incidence of adverse events was two times greater with dexmedetomidine 180 mcg or 120 mcg than placebo (36, 35, and 17 percent of patients). The most common side effects with active drug included

somnolence, dry mouth, hypotension, and dizziness. Although dexmedetomidine did not prolong the QT interval in this trial, other studies indicate that the drug can cause generally mild prolongation of the QT interval [47]. Thus, the drug should be avoided in patients at increased risk for QT prolongation, including patients taking other drugs that can prolong the QT interval (table 4). (See "Acquired long QT syndrome: Definitions, pathophysiology, and causes".)

Information about managing acute agitation in the emergency department is discussed separately. (See "Assessment and emergency management of the acutely agitated or violent adult", section on 'Management'.)

Decreased need for sleep — Patients with mania often present with a decreased need for sleep, and may feel rested after a few hours of sleep or may not sleep at all for several consecutive days; decreased need for sleep differs from insomnia, in which the individual wants to sleep but cannot [1]. We frequently include a benzodiazepine such as clonazepam or lorazepam in the medication regimen during the first week to promote sleep. (See 'Benzodiazepines' below.)

HYPOMANIA AND MILD TO MODERATE MANIA

Hypomania and mild to moderate mania are marked by the absence of suicidal or homicidal ideation or behavior, aggressiveness, psychotic features (ie, delusions or hallucinations), and poor judgment that places the patient or others at imminent risk of being harmed. Monotherapy is commonly used for initially treating hypomania and mild to moderate mania.

Approach to treatment — We suggest that acute treatment of hypomania and mild to moderate mania proceed according to the sequence described in the sections below. Patients begin with initial treatment and progress through each step until they respond. The duration of an adequate treatment trial is discussed separately. (See "Acute bipolar mania and hypomania in adults: General principles of pharmacotherapy", section on 'Duration of an adequate trial'.)

First-line monotherapy — Despite clinical differences between manic and hypomanic episodes (eg, hypomania is less severe than mania), they are treated with the same medications [2-9].

For patients with either hypomanic or mild to moderate manic episodes, we suggest monotherapy with risperidone or olanzapine, based upon efficacy and tolerability [33,34]. However, reasonable alternatives include aripiprazole, asenapine, carbamazepine, cariprazine, haloperidol, lithium, paliperidone, quetiapine, valproate, or ziprasidone. The use of risperidone, olanzapine, or the other drugs is consistent with multiple treatment guidelines [5-8,12,48].

Doses and side effects are discussed elsewhere in the topic. (See 'Medication doses and side effects' below.)

A network meta-analysis of 57 randomized trials (n >14,000 patients with an acute episode of pure mania or mania with mixed features, treated for three or four weeks) found that 12 standard drugs were each more efficacious than placebo: aripiprazole, asenapine, carbamazepine, cariprazine, haloperidol, lithium, olanzapine, paliperidone, quetiapine, risperidone, valproate, and ziprasidone [34]. The nonstandard medication tamoxifen was also more effective than placebo. Five drugs were no more effective than placebo: lamotrigine, licarbazepine, oxcarbazepine, topiramate, and verapamil.

In addition, the network meta-analysis ranked the 12 drugs by efficacy, using indirect comparisons of the drugs (through their relative effect with a common comparator, typically placebo), as well as analyzing direct comparisons between drugs [34]. Beginning with the most efficacious drug, the rank order for efficacy was:

- Risperidone
- Haloperidol
- Olanzapine
- Cariprazine
- Lithium
- Carbamazepine
- Paliperidone
- Aripiprazole
- Asenapine
- Quetiapine
- Ziprasidone
- Valproate (or divalproex)

Nevertheless, the probability of response (reduction of baseline symptoms ≥50 percent) was comparable across all the drugs.

The network meta-analysis also ranked the 12 drugs by frequency of treatment discontinuation for any reason, including adverse effects and lack of efficacy [34]. Beginning with the drug with the lowest rate of dropout, the rank order was:

- Olanzapine
- Risperidone
- Paliperidone
- Quetiapine

- Valproate
- Aripiprazole
- Ziprasidone
- Haloperidol
- Asenapine
- Carbamazepine
- Lithium
- Cariprazine

The indirect comparisons distinguish this network meta-analysis from smaller, conventional meta-analyses [13,15,49,50]. Although substantial uncertainties are introduced when these sorts of rank orders are created through the indirect comparisons that are used in a network meta-analysis, this may be the best evidence for comparing drugs for acute hypomania and mild to moderate mania. Network meta-analysis is discussed separately. (See "Systematic review and meta-analysis", section on 'Network meta-analysis'.)

Clinicians should consider other factors in addition to the rank order of efficacy and treatment discontinuation when choosing a drug, including the patient's past response to medications, the past response of family members with bipolar disorder to medications, specific manic symptoms, adverse drug effects, comorbid general medical illnesses, potential for drug-drug interactions, availability of specific drug preparations (eg, oral disintegrating), patient preference, and cost. As an example, patients with:

- Renal disease generally avoid lithium
- Liver disease generally avoid valproate
- Sensitivity to extrapyramidal symptoms generally avoid aripiprazole and risperidone
- Obesity generally avoid olanzapine, quetiapine, and risperidone

In addition, women of childbearing age generally avoid valproate.

Medication side effects are discussed separately.

- (See 'Medication doses and side effects' below.)
- (See "Bipolar disorder in adults and lithium: Pharmacology, administration, and management of adverse effects", section on 'Managing lithium adverse effects'.)
- (See "Antiseizure medications: Mechanism of action, pharmacology, and adverse effects".)
- (See "First-generation antipsychotic medications: Pharmacology, administration, and comparative side effects".)
- (See "Second-generation antipsychotic medications: Pharmacology, administration, and side effects".)

The long-term implications of choosing a drug also need to be considered; all patients with bipolar disorder should receive maintenance treatment, which commonly consists of the drug used to induce remission. As an example, maintenance lithium is common because it has been widely studied and is efficacious [51,52], and long-term treatment with lithium may reduce the risk of suicide attempts and deaths [53]. By contrast, haloperidol is generally not used in maintenance treatment because it can cause movement disorders and may increase the risk of bipolar major depression [54,55]. Although olanzapine is efficacious for pure mania as well as mania with mixed features [56], olanzapine is not a first-line drug for maintenance treatment because of concerns about weight gain and diabetes mellitus. Valproate is often not prescribed to women of childbearing potential because many pregnancies are unplanned and the drug is generally regarded as teratogenic [57]. Maintenance treatment is discussed separately. (See "Bipolar disorder in adults: Choosing maintenance treatment".)

For patients with hypomania or mild to moderate mania, who do not respond to treatment with one monotherapy trial within two weeks of reaching the target dose or do not tolerate the drug, we suggest tapering and discontinuing the failed medication over one week at the same time that another monotherapy is started and titrated up. The failed medication is generally tapered by the same amount for each dose decrease. As an example, quetiapine 600 mg per day is decreased by 100 to 200 mg per day, every one to two days.

Treatment resistance — For hypomanic and mild to moderate manic episodes that do not respond to three to five monotherapy trials involving aripiprazole, carbamazepine, haloperidol, lithium, olanzapine, quetiapine, risperidone, valproate, and ziprasidone, we suggest combining lithium or valproate with an antipsychotic [6,9,12]. However, lithium plus valproate is a reasonable alternative [9,12,58,59]. Medication combinations involving lithium or valproate plus an antipsychotic are discussed elsewhere in the topic. (See 'Initial treatment' above.)

Benzodiazepines — We suggest clonazepam for patients who have hypomanic or mild to moderate manic or mixed episodes and cannot tolerate lithium, anticonvulsants, or antipsychotics [6]. However, lorazepam is a reasonable alternative.

Benzodiazepine monotherapy is unusual due to the large number of available medication options for manic and hypomanic episodes; instead, benzodiazepines are generally used as adjunctive therapy to treat insomnia, agitation, or anxiety in patients with pathologic mood elevated syndromes [7,9]. Given the high rate of substance use disorders among bipolar patients and the potential for abusing benzodiazepines, these drugs are generally limited to acute treatment [60]. However, maintenance treatment with benzodiazepines is administered to catatonic patients who remit with benzodiazepines. (See "Catatonia: Treatment and prognosis", section on 'Benzodiazepine safety and administration'.)

Clonazepam is usually started at a dose of 1 to 3 mg per day, taken in two divided doses. The drug is generally titrated up to a target dose ranging from 2 to 6 mg per day, depending upon efficacy and tolerability, although doses as high as 24 mg per day have been used [61]. Side effects include disinhibition, sedation, and respiratory depression.

Lorazepam is usually started at a dose of 2 to 4 mg per day, taken in three to four divided doses. The drug is generally titrated up to a target dose ranging from 3 to 8 mg per day, depending upon efficacy and tolerability, although doses as high as 24 mg per day have been used [61]. Side effects include disinhibition, sedation, and respiratory depression.

Evidence of efficacy includes a meta-analysis of five randomized trials (122 manic patients) that compared clonazepam monotherapy (2 to 24 mg per day) with haloperidol, lithium, lorazepam, or placebo, and found that clonazepam was efficacious; however, heterogeneity across studies appeared to be substantial [61]. A meta-analysis of four randomized trials (108 manic patients) that compared lorazepam monotherapy (4 to 24 mg per day) with clonazepam, haloperidol, lithium, or placebo found that lorazepam was not effective [61]. However, one randomized trial directly compared lorazepam (mean daily dose 13 mg) with clonazepam (mean daily dose 14 mg) in 24 manic patients, and found that moderate to marked improvement occurred in more patients who received lorazepam than clonazepam (63 versus 18 percent), as did remission (38 versus 0 percent) [62]. The frequency of side effects did not differ between the clonazepam and lorazepam [61].

MEDICATION DOSES AND SIDE EFFECTS

Lithium — The starting dose of lithium is usually 300 mg two or three times daily; smaller doses (eg, 150 mg twice daily) are used in the elderly [60,63-65]. The dose should be increased by 300 to 600 mg every one to five days based upon response, tolerability, and body mass index. The goal is to reach a therapeutic serum level, which generally occurs with a dose of 900 mg to 1800 mg per day. Dose increases generally occur more frequently at the beginning of treatment, and less often as clinicians approach the target dose. Additional information about the dose of lithium is discussed elsewhere. (See "Bipolar disorder in adults and lithium: Pharmacology, administration, and management of adverse effects", section on 'Lithium dose and serum concentrations' and "Geriatric bipolar disorder: Treatment of mania and major depression", section on 'First-line medications'.)

The target serum level for acute treatment is between 0.8 and 1.2 mEq/L (0.8 and 1.2 mmol/L); levels should not exceed 1.2 mEq/L (1.2 mmol/L) to reduce the risk of toxicity [64]. Patients who cannot tolerate a level of 0.8 mEq/L (0.8 mmol/L) may respond to a level of 0.6 to 0.7 mEq/L (0.6

to 0.7 mmol/L). Lithium levels should be measured five to seven days after each dose increase. Levels are drawn 12 hours after the last dose (12-hour serum trough level) and generally collected in the morning, before the first dose of the day. Additional information about lithium serum levels is discussed elsewhere. (See "Bipolar disorder in adults and lithium: Pharmacology, administration, and management of adverse effects", section on 'Lithium dose and serum concentrations'.)

Lithium can cause many acute and long-term adverse effects. The most common acute side effects are nausea, tremor, polyuria and thirst, weight gain, loose stools, and cognitive impairment [65-67]. Severe or sudden worsening of acute side effects may be a sign of lithium toxicity. Over the long term, lithium can adversely affect the kidneys and thyroid gland. In addition, cardiac rhythm disturbances have been described; these almost always occur in patients with preexisting cardiac disease.

Additional information about lithium side effects and how to manage them, as well as contraindications to lithium, lithium toxicity, drug interactions with lithium, the different available preparations of lithium, and laboratory tests for monitoring patients treated with lithium is discussed separately. (See "Bipolar disorder in adults and lithium: Pharmacology, administration, and management of adverse effects", section on 'Managing lithium adverse effects' and "Lithium poisoning" and "Renal toxicity of lithium" and "Lithium and the thyroid".)

Anticonvulsants — Anticonvulsants that are efficacious for acute mania and hypomania include valproate and carbamazepine.

Suicidality — Bipolar disorder is associated with an increased risk of suicide deaths [68], and all patients should be monitored for emergence or worsening of suicidal thoughts and behavior. Although some observational studies suggest that anticonvulsants may increase the risk of suicidal ideation or behavior, these drugs are generally safe to use when patients are regularly monitored.

The US Food and Drug Administration warned clinicians that anticonvulsants are associated with an increased risk of suicidal thoughts and behavior, based upon a pooled analysis of 199 controlled trials that included patients with a variety of illnesses (total n >43,000) [69]. In addition, a separate exploratory analysis of a medical and pharmacy claims database that included 297,620 new episodes of treatment with an anticonvulsant suggested that gabapentin, lamotrigine, oxcarbazepine, and tiagabine may be associated with an increased risk of suicidal acts or violent deaths, compared with topiramate [70]. However, an observational study using data from a medical and pharmacy claims database of geriatric patients with a variety of illnesses (n >90,000) suggested that suicidal thoughts and behavior were more likely to occur

during the 30 days prior to initial use of an anticonvulsant than any other time period in the year before and after exposure [71].

In addition, an analysis of a different national claims database that involved patients diagnosed with bipolar disorder (n >47,000) found [72]:

- The frequency of suicide attempts in patients treated with antiseizure medications and patients not receiving antiseizure medications was comparable.
- For patients treated with antiseizure medications, the rate of suicide attempts was greater before treatment than after treatment.
- Patients receiving antiseizure medication monotherapy (and no concomitant antidepressant or antipsychotic) had fewer suicide attempts compared to patients receiving no pharmacotherapy.

Other observational studies have also found that antiseizure medications were not associated with an increased risk of suicidal behavior in bipolar patients [73]. As an example, analyses using a national database with over 5,000,000 patients found that among patients with bipolar disorder, treatment with antiseizure medications was not associated with an increased risk of suicide attempts [74].

Carbamazepine — Carbamazepine is usually started at a dose of 100 mg to 200 mg one or two times per day [75]. The dose should be increased by 200 mg per day every one to four days, to a final dose of about 800 to 1000 mg per day, although the effective dose may range between 200 and 1800 mg per day. Carbamazepine is typically administered twice daily. Therapeutic serum levels have not been established for treating acute manic episodes. However, many clinicians aim for a level of 4 to 12 mcg/mL, which is the target range established for treating epilepsy. Extended-release formulations are better tolerated in patients with bipolar disorder [76].

The major systemic side effects of carbamazepine are nausea, vomiting, diarrhea, hyponatremia, rash, pruritus, leukopenia, and fluid retention (table 5). Neurotoxicity includes drowsiness, dizziness, blurred or double vision, lethargy, and headache. Carbamazepine also induces liver enzymes and frequently causes drug-drug interactions that result in lower serum concentrations of concomitant drugs [60,77,78]. This induction of liver enzymes often decreases serum concentrations of carbamazepine. Liver function tests and a complete blood count, serum sodium, and serum carbamazepine level are recommended every 6 to 12 months.

In addition, the drug is associated with life-threatening rashes (Stevens-Johnson syndrome and toxic epidermal necrolysis), particularly during the first eight weeks of therapy (table 6) [79]. This reaction is significantly more common in patients with the HLA-B*1502 allele (estimated incidence of 5 percent), which occurs almost exclusively in Asian persons [80-82]. Screening for this allele is recommended in patients of this ethnic group prior to starting carbamazepine. (See "Stevens-Johnson syndrome and toxic epidermal necrolysis: Pathogenesis, clinical manifestations, and diagnosis", section on 'HLA polymorphism and pharmacogenetics'.)

The pharmacology of carbamazepine and its adverse effects and available preparations are discussed in greater detail elsewhere. (See "Antiseizure medications: Mechanism of action, pharmacology, and adverse effects", section on 'Carbamazepine'.)

Valproate or divalproex — Valproate is usually started at a dose of 500 or 750 mg per day; we typically use the delayed-release formulation of divalproex and initially administer it in two or three divided doses. The dose is increased by 250 mg to 500 mg every one to three days as tolerated to reach a therapeutic serum level, which generally occurs with 1500 mg to 2500 mg per day [65,83]. Once the daily dose is established, divalproex (either as a delayed-release or 24-hour extended release formulation) is typically given once daily at bedtime to improve adherence. If an immediate release formulation is needed (eg liquid), it can be given in two divided doses per day once the daily dose is established.

Oral loading and rapid titration to a full dose within one to two days by prescribing 20 mg/kg/day may result in earlier improvement in symptoms and a reduced need for adjunctive antipsychotics or benzodiazepines [2,7,84-87]. However, loading 20 mg/kg/day may cause intolerable side effects. In addition, for patients who are obese (eg, 120 kg), we rarely prescribe more than 2000 mg on day 1.

We suggest drawing valproate serum levels two to five days after each dose increase and prescribing the drug to achieve a target serum level between 50 and 125 mcg/mL. Levels should be drawn 8 to 12 hours after the last dose and generally collected in the morning, before the first dose of the day. When 24-hour extended-release preparations are administered in the morning, trough levels are drawn the following morning before the next daily dose [88]. When 24-hour extended-release preparations are administered at bedtime, levels are drawn 18 to 24 hours later, prior to the next dose. A post hoc analysis of pooled data from three controlled trials (374 acutely manic inpatients) found that efficacy increased as serum concentrations increased [89]. In addition, the efficacy of valproate was significantly greater than placebo for levels ≥71 mcg/mL, and the largest clinical effect for valproate occurred in patients with a mean serum concentration of 88 mcg/mL. After target serum levels have been achieved, levels should be checked at 6 to 12 month intervals, and are particularly useful in patients receiving

medications that affect valproate concentrations and to confirm problems with adherence. Some patients may not require regular valproate levels, and one review concluded that clinical observation of efficacy and toxicity can be used to guide some dose adjustments [90].

Common side effects of valproate include weight gain, nausea, vomiting, hair loss, easy bruising, and tremor (table 5). Divalproex is a formulation of valproate that can minimize gastrointestinal distress. In addition, valproate is rarely associated with hepatic failure and thrombocytopenia (table 6); liver function tests and platelets should thus be monitored at 6- to 12-month intervals in all patients taking the drug [60,77,78]. (The US Food and Drug Administration recommends checking liver function tests prior to initiating treatment and at frequent intervals thereafter, especially during the first six months.) In addition, valproate rarely causes pancreatitis; symptoms of abdominal pain and vomiting should prompt an assessment that includes a serum amylase and lipase.

Additional information about the pharmacology of valproate and its adverse effects and available preparations are discussed separately, as well as problems using valproate in women of childbearing age. (See "Bipolar disorder in women: Contraception and preconception assessment and counseling".)

Antipsychotics — First- and second-generation antipsychotics are efficacious for treating both psychotic and nonpsychotic manic and hypomanic episodes [6,13-15,49].

First-generation — Among first-generation antipsychotics, we prefer haloperidol for treating manic episodes because it has been widely studied and generally causes less orthostatic hypotension and sedation than chlorpromazine, which is also efficacious [50,91]. Other first-generation antipsychotics such as fluphenazine, loxapine, perphenazine, thiothixene, and trifluoperazine are effective as well [92].

We suggest patients initially receive haloperidol at a dose of 2 to 15 mg per day, depending upon the severity of symptoms, the patient's body mass index, and adverse effects that emerge. The drug is taken either once per day or in two divided doses, depending upon tolerability and the patient's ability to adhere to treatment with divided doses. One useful guide is to initially prescribe 0.2 mg per kg per day [93]. In a meta-analysis of 15 randomized trials (2022 acutely ill patients with pure mania or mania with mixed features), which found that haloperidol was comparable to carbamazepine, olanzapine, risperidone, and valproate, the dose of haloperidol ranged from 2 to 85 mg per day [50].

Conventional antipsychotics are associated with extrapyramidal symptoms, akathisia, and tardive dyskinesia. Extrapyramidal symptoms are usually managed by lowering the dose of the

antipsychotic or by adding an anticholinergic drug, either benztropine 1 to 2 mg two to four times daily or trihexyphenidyl 2 to 5 mg two to four times daily.

Although switching from mania to depression has been attributed to first-generation antipsychotics, the evidence is not clear. A meta-analysis of six randomized trials (1774 manic patients) compared haloperidol with second-generation antipsychotics (aripiprazole, olanzapine, quetiapine, risperidone, or ziprasidone), and found that treatment emergent depression was comparable for patients who received haloperidol or second-generation antipsychotics (10 and 7 percent); heterogeneity across studies was moderate [94]. However, a second analysis that excluded one outlier trial (and eliminated the heterogeneity) found that depressive switches occurred in more patients treated with haloperidol (12 versus 7 percent). In assessing patients treated with an antipsychotic, clinicians should distinguish between switching to a depressive syndrome and the side effect of affective blunting or flattening.

The pharmacology, administration, and side effects of first-generation antipsychotics are discussed elsewhere. (See "First-generation antipsychotic medications: Pharmacology, administration, and comparative side effects" and "Tardive dyskinesia: Etiology, risk factors, clinical features, and diagnosis" and "Neuroleptic malignant syndrome".)

Second-generation — Aripiprazole, olanzapine, quetiapine, risperidone, and ziprasidone are each efficacious for treating mania and hypomania [33], and the choice often depends upon differences in adverse side effects (table 7). Metabolic problems such as weight gain, glucose intolerance, diabetes mellitus, and hyperlipidemia are most likely to occur with olanzapine, followed by quetiapine and risperidone. Thus, patients taking olanzapine, quetiapine, and risperidone should be regularly monitored for weight, waist circumference, blood pressure, and serum glucose and lipids (table 8). Extrapyramidal symptoms are more common with aripiprazole, olanzapine, risperidone, or ziprasidone compared with quetiapine. The metabolic syndrome and extrapyramidal symptoms are discussed separately. (See "Metabolic syndrome (insulin resistance syndrome or syndrome X)" and "Schizophrenia in adults: Maintenance therapy and side effect management", section on 'Extrapyramidal symptoms' and "Schizophrenia in adults: Maintenance therapy and side effect management", section on 'Metabolic dysregulation'.)

The usual starting and target dose for second-generation antipsychotics that were used in randomized monotherapy trials for mania, and side effects that commonly occurred, are described below [10,95-101]. Target doses can generally be achieved within one week of starting the medication. Some drugs are available as oral dissolvable formulations for patients who pretend to swallow their pills (“cheek”) and spit them out later when clinicians are not looking.

- **Aripiprazole** – Aripiprazole is started at a dose of 10 to 30 mg once daily, and is generally titrated in increments of 5 to 10 mg/day at intervals ≥1 week. The usual target dose is 15 to 30 mg taken once per day. Common side effects include headache, nausea, vomiting, constipation, insomnia, and akathisia. An oral dissolvable formulation is available.

- **Asenapine** – Asenapine is started at 5 or 10 mg twice daily on day 1, and thereafter dosed at 5 or 10 mg two times per day. Some patients may respond to a total daily dose of 15 mg per day, split between two doses. Common side effects include sedation, fatigue, dizziness, extrapyramidal symptoms, vomiting, dry mouth, and weight gain.

- **Cariprazine** – The standard dose range for cariprazine is 3 to 12 mg/day once daily. On day 1 the dose is 1.5 mg/day, and on day 2 the dose is 3 mg/day. Depending upon response and tolerability, the dose is subsequently increased by increments of 1.5 or 3 mg/day to a maximum of 12 mg/day. Adverse effects of cariprazine that occur in at least 5 percent of patients and at least twice as often as placebo include akathisia, extrapyramidal symptoms, restlessness, and vomiting. Mean weight change during three weeks of treatment with cariprazine or placebo are 0.5 kg.

- **Olanzapine** – Olanzapine is started at a dose of 10 to 15 mg once daily or in two divided doses. The usual target dose is 10 to 30 mg per day, taken at bedtime or in two divided doses. Some patients may require and tolerate 40 or 50 mg per day. Common side effects include sedation, constipation, dry mouth, increased appetite, weight gain, and orthostatic hypotension. An oral dissolvable formulation is available.

- **Paliperidone** – The standard dose range for paliperidone is 3 to 12 mg/day once daily. Paliperidone is started at either 3 or 6 mg/day on day 1; thereafter, the dose is titrated up by increments of 3 mg/day every one to three days to a maximum of 12 mg/day, depending upon response and tolerability. The most common adverse events are headache, somnolence, dizziness, akathisia, hypertonia, and dyspepsia.

- **Quetiapine** – Quetiapine immediate release is started at a dose of 100 to 200 mg once daily or in two divided doses. The usual target dose is 400 to 800 mg taken at bedtime or in two divided doses. Some patients may require and tolerate 1000 or 1200 mg per day. Common side effects include headache, dry mouth, constipation, weight gain, sedation, dizziness, and orthostatic hypotension.

- **Risperidone** – Risperidone is started at a dose of 1 to 2 mg once daily or in two divided doses. The usual target dose is 4 to 8 mg per day. It is usually taken in two divided doses per day, but some patients may do well with a single dose at bedtime. Common side

effects include prolactin elevation, akathisia, sedation, dyspepsia, nausea, and weight gain. An oral dissolvable formulation is available.

- **Ziprasidone** – Ziprasidone is started at a dose of 40 mg two times per day. The usual target dose is 40 to 80 mg two times per day. Some patients may require and tolerate larger doses; although doses of 320 mg/day have been studied, we suggest a maximum dose of 240 mg/day. Common side effects include headache, sedation, extrapyramidal symptoms, akathisia, and dizziness.

Additional information about second-generation antipsychotics is discussed separately. (See "Second-generation antipsychotic medications: Pharmacology, administration, and side effects".)

TREATING SPECIFIC SUBGROUPS

Rapid cycling patients — Pharmacotherapy for mania and hypomania that occur in the context of rapid cycling is discussed separately. (See "Rapid cycling bipolar disorder in adults: Treatment of mania and hypomania".)

Pregnant patients — Pharmacotherapy for antenatal mania and hypomania is discussed separately. (See "Bipolar disorder in pregnant women: Screening, diagnosis, and choosing treatment for mania and hypomania".)

Postpartum patients — Pharmacotherapy for postnatal mania and hypomania is discussed separately. (See "Bipolar disorder in postpartum women: Treatment".)

Geriatric patients — Pharmacotherapy for late-life mania and hypomania is discussed separately. (See "Geriatric bipolar disorder: Treatment of mania and major depression", section on 'Mania and hypomania'.)

Pediatric patients — Pharmacotherapy for pediatric mania and hypomania is discussed separately. (See "Pediatric bipolar disorder: Overview of choosing treatment".)

INDICATIONS FOR REFERRAL

Although some primary care clinicians have the requisite training and experience to manage bipolar disorder, many patients are referred to psychiatrists and other mental health clinicians if these specialists are available. Common indications for referral include:

- Suicidal ideation and behavior
- Psychotic features (eg, auditory hallucinations commanding patients to kill themselves)
- Fluctuating symptoms
- Impulsive and dangerous behavior
- Functional impairment
- Comorbid psychopathology (eg, anxiety disorders and substance use disorders)
- Multiple (eg, two to four) failed medication trials
- Administration of adjunctive psychotherapy
- Recurrence of mood episodes

Primary care clinicians who refer patients to specialists are encouraged to remain involved in management. General internists and other clinicians can help educate patients and families about pharmacotherapy and reinforce the need for adherence, and typically collaborate in evaluating patients prior to treatment and monitoring vital signs, weight, height, and waist size during treatment.

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)")

Additional information for patients is discussed separately. (See "Acute bipolar mania and hypomania in adults: General principles of pharmacotherapy", section on 'Information for patients'.)

SUMMARY AND RECOMMENDATIONS

- **Definition of bipolar disorder** – Bipolar disorder is characterized by episodes of mania (table 1), hypomania (table 2), and major depression (table 3). (See 'Definition of bipolar disorder' above.)

- **General treatment principles** – The general principles and issues that are involved in treating acute bipolar mania and hypomania include the nature of the evidence, similar approach for mania and hypomania, assessment and monitoring, level of care, goals, drug classes, duration of an adequate trial, predictors of response, relapse during maintenance treatment, destabilizing drugs, and indications for referral. (See "Acute bipolar mania and hypomania in adults: General principles of pharmacotherapy".)

- **Severe manic episodes**

  - **Initial treatment** – For patients with severe mania, we suggest initial treatment with lithium or valproate plus an antipsychotic, rather than monotherapy with lithium, valproate, or an antipsychotic (algorithm 1) (**Grade 2B**). We generally combine lithium or valproate with aripiprazole, haloperidol, olanzapine, quetiapine, or risperidone. (See 'Initial treatment' above and 'Medication doses and side effects' above.)

  - **Treatment-resistant patients** – For patients with severe, treatment-resistant mania that does not respond to one medication combination (lithium or valproate plus an antipsychotic), we suggest additional medication combination trials rather than electroconvulsive therapy (**Grade 2B**). Lithium is switched to valproate (or vice versa), and the antipsychotic is switched to another antipsychotic. (See 'Treatment-resistant patients' above.)

  - **Treatment-refractory patients** – For treatment-refractory patients with severe mania who do not respond to four to six medication combinations, we suggest

electroconvulsive therapy rather than additional trials of pharmacotherapy combinations (**Grade 2C**). (See 'Treatment-refractory patients' above.)

- **Hypomania or mild to moderate mania**

  - **Initial treatment** – For patients with acute hypomania or mild to moderate mania, we suggest initial treatment with risperidone or olanzapine monotherapy rather than other drugs (**Grade 2B**). However, reasonable alternatives include aripiprazole, asenapine, carbamazepine, cariprazine, haloperidol, lithium, paliperidone, quetiapine, valproate, or ziprasidone. In addition to efficacy and tolerability, the choice depends upon past response to medications, comorbid medical illness, concurrent medications, specific symptoms, and cost. (See 'First-line monotherapy' above.)

  - **Treatment resistance** – For patients with hypomania or mild to moderate mania that does not respond to three to five monotherapy drug trials, we suggest combining either lithium or valproate with an antipsychotic (other than ziprasidone) rather than additional monotherapy trials (**Grade 2C**). Another option is using lithium plus valproate. (See 'Initial treatment' above.)

- **Treating specific subgroups** – Choosing pharmacotherapy for treating acute mania and hypomania in specific subgroups is discussed elsewhere:

  - (See "Rapid cycling bipolar disorder in adults: Treatment of mania and hypomania".)
  - (See "Bipolar disorder in pregnant women: Screening, diagnosis, and choosing treatment for mania and hypomania".)
  - (See "Bipolar disorder in postpartum women: Treatment".)
  - (See "Geriatric bipolar disorder: Treatment of mania and major depression", section on 'Mania and hypomania'.)
  - (See "Pediatric bipolar disorder: Overview of choosing treatment".)

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