TREATING
BIPOLAR DISORDER
A Quick Reference Guide

Based on *Practice Guideline for the Treatment of Patients With Bipolar Disorder,* Second Edition, originally published in April 2002. A guideline watch, summarizing significant developments in the scientific literature since publication of this guideline, may be available in the Psychiatric Practice section of the APA web site at www.psych.org.

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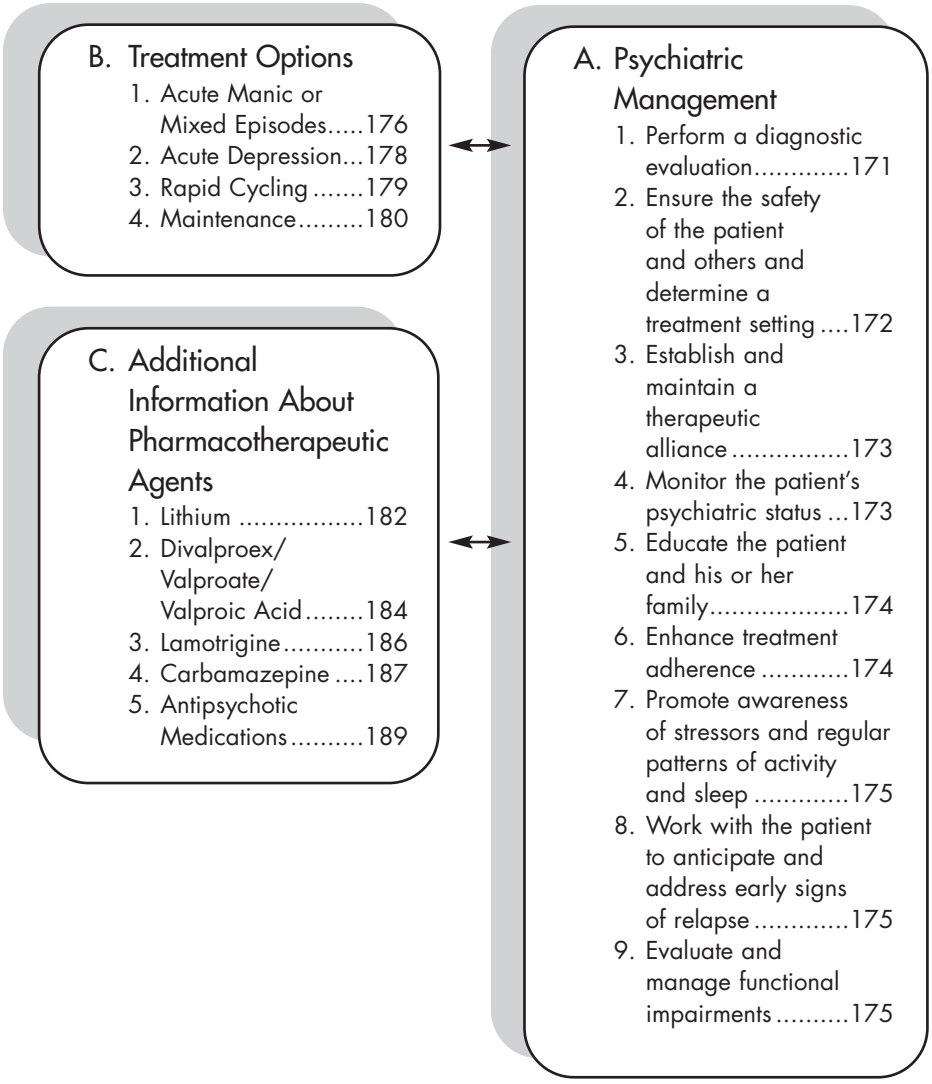
The Practice Guidelines and the Quick Reference Guides are not intended to be construed or to serve as a standard of medical care. Standards of medical care are determined on the basis of all clinical data available for an individual patient and are subject to change as scientific knowledge and technology advance and practice patterns evolve. These parameters of practice should be considered guidelines only. Adherence to them will not ensure a successful outcome for every individual, nor should they be interpreted as including all proper methods of care or excluding other acceptable methods of care aimed at the same results. The ultimate judgment regarding a particular clinical procedure or treatment plan must be made by the psychiatrist in light of the clinical data presented by the patient and the diagnostic and treatment options available.

The development of the APA Practice Guidelines and Quick Reference Guides has not been financially supported by any commercial organization. For more detail, see APA's "Practice Guideline Development Process," available as an appendix to the compendium of APA practice guidelines, published by APPI, and online at http://www.psych.org/psych_pract/treatg/pg/prac_guide.cfm.

OUTLINE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A. Psychiatric Management

Goals of Psychiatric Management
- Establish and maintain a therapeutic alliance.
- Monitor the patient's psychiatric status.
- Provide education regarding bipolar disorder.
- Enhance treatment adherence.
- Promote regular patterns of activity and sleep.
- Anticipate stressors.
- Identify new episodes early.
- Minimize functional impairments.

1. Perform a diagnostic evaluation.

Assess for the presence of an alcohol or substance use disorder or other factors that may contribute to the disease process or complicate its treatment.
- Neurological conditions commonly associated with secondary mania are multiple sclerosis and lesions involving right-sided subcortical structures or cortical areas closely linked to the limbic system.
- L-Dopa and corticosteroids are the most common medications associated with secondary mania.
- Substance use may precipitate mood episodes. Patients may also use substances to ameliorate the symptoms of such episodes.

Inquire about a history of time periods with mood dysregulation or lability accompanied by associated manic symptoms (e.g., decreased sleep).
- Bipolar disorder commonly presents with depressive symptoms.
- Patients rarely volunteer information about manic or hypomanic symptoms.

2. Ensure the safety of the patient and others and determine a treatment setting.

Evaluate safety.

- Careful assessment of the patient's risk for suicide is critical; lifetime rates of completed suicide for people with bipolar disorder are as high as 10% to 15%.
- The overwhelming majority of suicide attempts are associated with depressive episodes or depressive features during mixed episodes.
- Ask every patient about suicidal ideation, intention to act on these ideas, and extent of plans or preparation for suicide.
- Collect collateral information from family members or others.
- Assess for access to means of committing suicide (e.g., medications, firearms) and the lethality of these means.
- Assess for factors associated with increased risk, such as agitation, pervasive insomnia, impulsiveness, or other psychiatric comorbidity such as substance abuse, psychosis (especially with command hallucinations), or personality disorder.
- Assess for family history of suicide and history of recent exposure to suicide.
- Consider the nature and potential lethality of any prior suicide attempts.
- Closely monitor patients who exhibit suicidal or violent ideas or intent.
- Carefully document the decision-making process.

Consider hospitalization for patients who

- pose a serious threat of harm to themselves or others,
- are severely ill and lack adequate social support outside a hospital setting or demonstrate significantly impaired judgment,
- have complicating psychiatric or general medical conditions, or
- have not responded adequately to outpatient treatment.

Reevaluate the treatment setting on an ongoing basis to determine whether it is optimal or whether the patient would benefit more from a different level of care.

Provide a calm and highly structured environment.

Consider limiting access to cars, credit cards, bank accounts, or telephones and cellular phones during the manic phase because of the risk of reckless behavior.

3. Establish and maintain a therapeutic alliance.

- A therapeutic alliance is critical for understanding and managing the individual patient.
- Over time, knowledge gained about the patient and the illness course allows early identification of usual prodromal symptoms and early recognition of new episodes.

4. Monitor the patient's psychiatric status.

- Monitoring is especially important during manic episodes, when patient insight is often limited or absent.
- Be aware that small changes in mood or behavior may herald the onset of an episode.

5. Educate the patient and his or her family.

- Be aware that, over time, patients will vary in their ability to understand and retain information and accept and adapt to the need for long-term treatment.
- Education should be an ongoing process in which the psychiatrist gradually but persistently introduces facts about the illness and its treatment.
- Printed and Internet material (e.g., from www.psych.org) can be helpful.
- Use similar educational approaches for family members and significant others.

6. Enhance treatment adherence.

- Ambivalence about treatment is often expressed as poor adherence to medication or other treatments.
- Causes of ambivalence include
  - lack of insight about having a serious illness and
  - reluctance to give up the experience of hypomania or mania.
- Medication side effects, cost, and other demands of long-term treatment may be burdensome and need to be discussed.
- Many side effects can be corrected with careful attention to dosing, scheduling, and medication formulation (e.g., sustained release, liquid).

7. Promote awareness of stressors and regular patterns of activity and sleep.

- Stressors commonly precede episodes in all phases of the illness.
- Social rhythm disruption with disrupted sleep-wake cycles may specifically trigger manic episodes.
- Patients and their families should be informed about the potential effects of sleep disruption in triggering manic episodes.
- Regular patterns for daily activities should be promoted, including sleeping, eating, physical activity, and social and emotional stimulation.

8. Work with the patient to anticipate and address early signs of relapse.

- The psychiatrist should help the patient, family members, and significant others recognize early signs and symptoms of manic or depressive episodes.
- Early markers of episode onset are often predictable across episodes for an individual patient.
- Early identification of a prodrome is facilitated by the psychiatrist's consistent relationship with the patient as well as with the patient's family.

9. Evaluate and manage functional impairments.

Identify and address impairments in functioning.

- Assist the patient in scheduling absences from work or other responsibilities.
- Encourage the patient to avoid major life changes while in a depressive or manic state.
- Assess and address the needs of children of patients with bipolar disorder.

B. Treatment Options

1. Acute Manic or Mixed Episodes

Goals of Treatment

- Control symptoms to allow a return to usual levels of psychosocial functioning.
- Rapidly control agitation, aggression, and impulsivity.

→ **Choose an initial treatment modality.**

→ **For patients not yet in treatment for bipolar disorder:**

For *severe mania or mixed episodes,* initiate lithium in combination with an antipsychotic or valproate in combination with an antipsychotic.

For *less ill patients,* monotherapy with lithium, valproate, or an antipsychotic such as olanzapine may be sufficient.

- Short-term adjunctive treatment with a benzodiazepine may also be helpful.
- For mixed episodes, valproate may be preferred over lithium.
- Second-generation (atypical) antipsychotics are preferred over first-generation (typical) antipsychotics because of their generally more tolerable side effect profile.
- Alternatives include 1) carbamazepine or oxcarbazepine in lieu of lithium or valproate and 2) ziprasidone or quetiapine in lieu of another antipsychotic.
- Treatment selection depends on illness severity, associated features such as rapid cycling or psychosis, and, where possible, patient preference.
- Antidepressants should be tapered and discontinued if possible.
- Psychosocial therapies and pharmacotherapies should be combined.

For patients who suffer a "breakthrough" manic or mixed episode while on maintenance treatment, optimize the medication dose.

- Ensure that serum levels are within the therapeutic range; in some instances, achieve a higher serum level (but still within the therapeutic range).
- Introduction or resumption of an antipsychotic is often necessary.
- Severely ill or agitated patients may also require short-term adjunctive treatment with a benzodiazepine.

If symptoms are inadequately controlled within 10 to 14 days of treatment with optimized doses of the first-line medication regimen, add another first-line medication.

- Alternative treatment options include adding carbamazepine or oxcarbazepine in lieu of an additional first-line medication (lithium, valproate, antipsychotic), adding an antipsychotic if not already prescribed, or changing from one antipsychotic to another.
- Clozapine may be particularly effective in refractory illness.
- Electroconvulsive therapy (ECT) may also be considered for
  - manic patients who are severely ill or whose mania is treatment resistant;
  - patients who, after consultation with the psychiatrist, prefer ECT;
  - patients with mixed episodes; and
  - patients with severe mania during pregnancy.

For psychosis during a manic or mixed episode, treat with an antipsychotic medication.

- Second-generation antipsychotics are favored because of their generally more tolerable side effect profile.
- ECT may also be considered.

2. Acute Depression

Goals of Treatment

- Achieve remission of the symptoms of major depression and return the patient to usual levels of psychosocial functioning.
- Avoid precipitating a manic or hypomanic episode.

Choose an initial treatment modality.

For patients not yet in treatment for bipolar disorder, initiate either lithium or lamotrigine.

- As an alternative, especially for more severely ill patients, consider initiating treatment with both lithium and an antidepressant simultaneously (although supporting data are limited).
- Antidepressant monotherapy is not recommended.
- Consider ECT for
  - patients with life-threatening inanition, suicidality, or psychosis or
  - severe depression during pregnancy.
- Treatment selection should be guided by illness severity, associated features such as rapid cycling or psychosis, and, where possible, patient preference.
- Interpersonal therapy and cognitive behavior therapy may be useful when added to pharmacotherapy.
- Although psychodynamic psychotherapy for bipolar depression has not been empirically studied, it is widely used in combination with medication.

For patients who suffer a breakthrough depressive episode while on maintenance treatment, optimize the medication dosage. Ensure that serum levels are within the therapeutic range; in some instances, achieve a higher serum level (but still within the therapeutic range).

If the patient fails to respond to optimized maintenance treatment, consider adding lamotrigine, bupropion, or paroxetine.

- Alternative next steps include adding another newer antidepressant (e.g., another selective serotonin reuptake inhibitor [SSRI] or venlafaxine) or a monoamine oxidase inhibitor (MAOI).
- Tricyclic antidepressants may carry a greater risk of precipitating a switch and are not recommended.
- MAOIs may be difficult to use because of the risk of severe drug and dietary interactions.
- Psychotic features during depression usually require adjunctive treatment with an antipsychotic medication. Some evidence suggests efficacy for antipsychotic medication (e.g., olanzapine, quetiapine) in treating nonpsychotic bipolar depression.
- Consider ECT for
  - severe or treatment-resistant depression,
  - psychotic features, or
  - catatonic features.
- Clinicians may elect to use antidepressants earlier for bipolar II depression than for bipolar I depression because patients with bipolar II disorder probably have lower rates of antidepressant-induced switching into hypomania or mania.

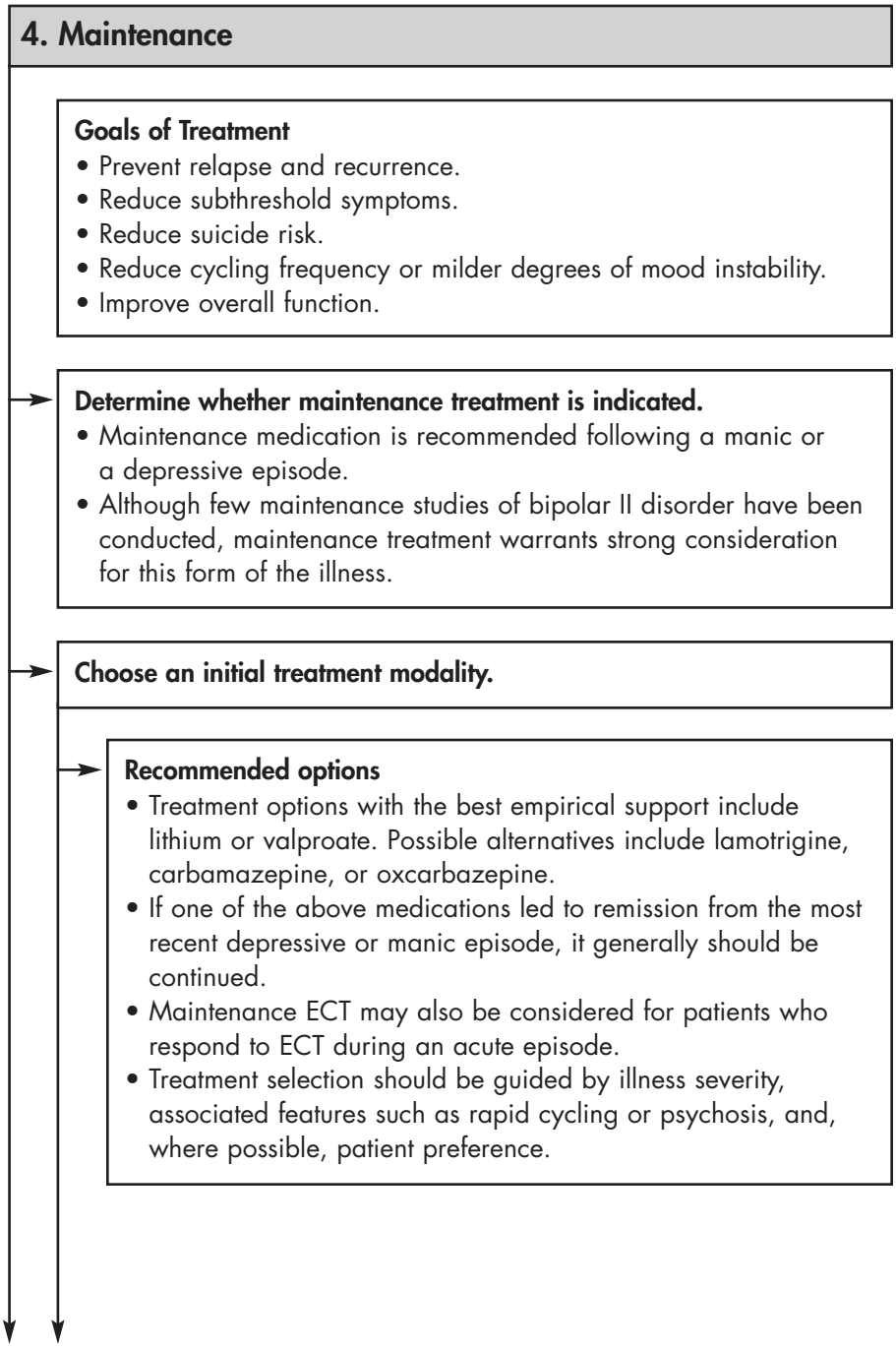
3. Rapid Cycling

Identify and treat medical conditions such as hypothyroidism or drug or alcohol use that may contribute to cycling.

If possible, taper medications (particularly antidepressants) that may contribute to cycling.

For initial treatment, include lithium or valproate.

- An alternative treatment is lamotrigine.
- For many patients, combinations of medications are required (i.e., combining two of the agents above or one of them plus an antipsychotic).


4. Maintenance
Goals of Treatment
• Prevent relapse and recurrence.
• Reduce subthreshold symptoms.
• Reduce suicide risk.
• Reduce cycling frequency or milder degrees of mood instability.
• Improve overall function.
Determine whether maintenance treatment is indicated.
• Maintenance medication is recommended following a manic or a depressive episode.
• Although few maintenance studies of bipolar II disorder have been conducted, maintenance treatment warrants strong consideration for this form of the illness.
Choose an initial treatment modality.
Recommended options
• Treatment options with the best empirical support include lithium or valproate. Possible alternatives include lamotrigine, carbamazepine, or oxcarbazepine.
• If one of the above medications led to remission from the most recent depressive or manic episode, it generally should be continued.
• Maintenance ECT may also be considered for patients who respond to ECT during an acute episode.
• Treatment selection should be guided by illness severity, associated features such as rapid cycling or psychosis, and, where possible, patient preference.

Role of antipsychotics

- Antipsychotic medications should be discontinued unless they are needed for control of persistent psychosis or prevention of recurrence of mood episodes.
- Maintenance therapy with second-generation antipsychotics may be considered, but there is less evidence that their efficacy in maintenance treatment is comparable to that of the other agents discussed above.

Role of psychosocial interventions

- Concomitant psychosocial interventions addressing illness management (i.e., adherence, lifestyle changes, and early detection of prodromal symptoms) and interpersonal difficulties are likely to be of benefit.
- Supportive and psychodynamic psychotherapies are widely used in combination with medication.
- Group psychotherapy and family therapy may also help patients address issues such as adherence to a treatment plan, adaptation to a chronic illness, regulation of self-esteem, and management of marital and other psychosocial issues.
- Support groups provide useful information about bipolar disorder and its treatment.

If the patient fails to respond (i.e., continues to experience subthreshold symptoms or breakthrough mood episodes), add another maintenance medication, a second-generation antipsychotic, or an antidepressant.

- There are insufficient data to support one combination over another.
- Maintenance ECT may also be considered for patients who respond to ECT during an acute episode.

C. Additional Information About Pharmacotherapeutic Agents

1. Lithium

Side effects

- Up to 75% of patients experience some side effects, but most side effects either are minor or can be reduced or eliminated by lowering the lithium dose or changing the dosage schedule.
- Side effects related to peak serum levels (e.g., tremor within 1 to 2 hours of a dose) may be reduced or eliminated by using a slow-release preparation or changing to a single bedtime dose.
- Side effects include polyuria, polydypsia, weight gain, cognitive problems, tremor, sedation or lethargy, impaired coordination, gastrointestinal distress, hair loss, benign leukocytosis, acne, and edema.
- With long-term lithium treatment (>10 years), 10% to 20% of patients display morphological kidney changes. These changes are not generally associated with renal failure, although there are some case reports of renal insufficiency probably induced by lithium.
- Most patients experience some toxic effects with levels above 1.5 meq/L; levels above 2.0 meq/L are commonly associated with life-threatening side effects. At higher serum levels, hemodialysis may be needed to minimize toxicity.

Implementation

Initial workup

The following are generally recommended before beginning lithium therapy:

- General medical history and physical examination
- Blood urea nitrogen (BUN) and creatinine levels
- Tests of thyroid function
- Electrocardiogram (ECG) with rhythm strip for patients over age 40
- Pregnancy test (in women of childbearing age)

Dosing

- Start in low divided dosages to minimize side effects (e.g., 300 mg t.i.d. or less, depending on the patient's weight and age).
- Titrate dosage upward (generally to serum concentrations of 0.5 to 1.2 meq/L) according to response and side effects.
- Check lithium level after each dosage increase (steady-state levels are likely to be reached approximately 5 days after a dosage adjustment).
- Check at shorter intervals after dosage increase as levels approach upper limits of the therapeutic range (i.e., greater than 1.0 meq/L).
- The "optimal" maintenance level may vary from patient to patient. Some patients require the level used to treat acute mania; others can be satisfactorily maintained at lower levels.

Long-term monitoring of laboratory values

- Serum lithium levels
  - At minimum, check every 6 months in stable patients and whenever the clinical status changes.
  - The optimal frequency of monitoring depends on the stability of lithium levels over time for that patient and the degree to which the patient can be relied on to notice and report symptoms.
- Renal function
  - In general, during the first 6 months of treatment, test every 2 to 3 months.
  - Subsequently, check every 6 to 12 months in stable patients as well as whenever the clinical status changes.
- Thyroid function
  - In general, during the first 6 months of treatment, test once or twice.
  - Subsequently, check every 6 to 12 months in stable patients and whenever the clinical status changes.

2. Divalproex/Valproate/Valproic Acid

Side effects

- Common dose-related side effects of valproate include gastrointestinal distress, benign hepatic transaminase elevations, osteoporosis, tremor, and sedation.
- Patients with past or current hepatic disease may be at increased risk for hepatotoxicity.
- Mild, asymptomatic leukopenia and thrombocytopenia occur less frequently and are reversible on drug discontinuation.
- Other side effects include hair loss, increased appetite, and weight gain.
- Although risks are unclear, female patients should be monitored for possible development of polycystic ovarian syndrome.
- Rare, idiosyncratic, but potentially fatal adverse events include irreversible hepatic failure, hemorrhagic pancreatitis, and agranulocytosis; patients should be educated about the signs and symptoms of hepatic and hematological dysfunction and warned to contact their physician immediately if symptoms develop.

Implementation

Initial workup

The following are generally recommended before beginning valproate therapy:

- Before treatment, take a general medical history with special attention to hepatic, hematological, and bleeding abnormalities.
- Obtain liver function tests and hematological measures.

Dosing

- For hospitalized patients with acute mania, valproate can be administered at an initial dosage of 20 to 30 mg/kg per day in inpatients. After obtaining a valproate level, adjust the dose to achieve a serum level between 50 and 125 μg/mL.
- For outpatients, elderly patients, or patients with hypomania or euthymia, start at 250 mg t.i.d. Titrate the dose upward by 250 to 500 mg/day every few days, depending on clinical response and side effects, generally to a serum concentration of 50 to 125 μg/mL, with a maximum adult daily dosage of 60 mg/kg per day. Once the patient is stable, simplify to once- or twice-daily dosing.
- Bioavailability of the extended-release preparation, divalproex ER, is about 15% less than that of the immediate-release preparation; doses of divalproex ER will need to be increased proportionately.

Drug interactions

- Valproate displaces highly protein-bound drugs from their protein binding sites. Dosage adjustments will be needed.
- Because valproate inhibits lamotrigine metabolism, lamotrigine must be initiated at less than half the usual dose.

Long-term monitoring of laboratory values

- Patients should be educated about the signs and symptoms of hepatic and hematological dysfunction and instructed to report these symptoms if they occur.
- Most psychiatrists perform clinical assessments, including tests of hematological and hepatic function, at a minimum of every 6 months for stable patients who are taking valproate.
- Serum levels of valproic acid should be checked when clinically indicated (e.g., when another medication may change the metabolism of valproic acid).

3. Lamotrigine

Side effects

- The most common side effects are headache, nausea, infection, and xerostomia.
- In early clinical trials with patients with epilepsy, rapid titration of lamotrigine dosage was associated with a risk of serious rash, including Stevens-Johnson syndrome and toxic epidermal necrolysis. Risk was approximately 0.3% in adults and approximately 1% in children.
- Patients should be informed of the risk of rash and of the need to contact the psychiatrist or primary care physician immediately if any rash occurs.
- Rash can occur at any time during treatment but is more likely early in treatment.
- At rash onset, it is difficult to distinguish between a serious and a more benign rash.
- Particularly worrisome, however, are rashes accompanied by fever or sore throat, those that are diffuse and widespread, and those with prominent facial or mucosal involvement. In such circumstances, lamotrigine (and valproate, if administered concurrently) should be discontinued.
- In clinical trials, use of a slow dosage titration schedule (see below) reduced the risk of serious rash in adults to 0.01% (comparable to other anticonvulsants).
- Rash may be more likely if lamotrigine and valproate are administered concomitantly.

Implementation

- Lamotrigine should be administered at 25 mg/day for the first 2 weeks, then at 50 mg for weeks 3 and 4.
- After that, 50 mg/week can be added as clinically indicated.
- To minimize the risk of potentially serious rash in patients who are receiving valproate, the dose or the dosage schedule should be halved (i.e., 12.5 mg/day or 25 mg every other day for 2 weeks, then 25 mg daily for weeks 3 and 4).
- Concurrent carbamazepine treatment will lead to increased metabolism of lamotrigine and will require that dosing be doubled.

4. Carbamazepine

Side effects

- Up to 50% of patients receiving carbamazepine experience side effects.
- The most common side effects include fatigue, nausea, and neurological symptoms such as diplopia, blurred vision, and ataxia.
- Less frequent side effects include skin rashes, mild leukopenia, mild liver enzyme elevations, mild thrombocytopenia, hyponatremia, and (less commonly) hypo-osmolality.
- Rare, idiosyncratic, but serious and potentially fatal side effects include agranulocytosis, aplastic anemia, thrombocytopenia, hepatic failure, exfoliative dermatitis (e.g., Stevens-Johnson syndrome), and pancreatitis.
- In addition to careful monitoring of clinical status, it is essential to educate patients about the signs and symptoms of hepatic, hematological, or dermatological reactions and instruct them to report symptoms if they occur.
- Other rare side effects include systemic hypersensitivity reactions; cardiac conduction disturbances; psychiatric symptoms, including sporadic cases of psychosis; and, very rarely, renal effects, including renal failure, oliguria, hematuria, and proteinuria.
- The carbamazepine analogue oxcarbazepine may be a useful alternative to carbamazepine based on its superior side effect profile.

4. Carbamazepine *(continued)*

Implementation

Initial workup

The following are generally recommended before beginning carbamazepine therapy:

- Minimum baseline evaluation should include a complete blood count (CBC) with differential and platelet count, a liver profile (LDH, SGOT, SGPT, bilirubin, alkaline phosphatase), and renal function tests. Serum electrolytes may also be obtained, especially in the elderly, who may be at higher risk for hyponatremia.
- Before treatment, a general medical history and a physical examination should be done, with special emphasis on prior history of blood dyscrasias or liver disease.

Dosing

- Carbamazepine is usually begun at a total daily dose of 200 to 600 mg, in three to four divided doses.
- In hospitalized patients with acute mania, the dosage may be increased in increments of 200 mg/day up to 800 to 1000 mg/day (unless side effects develop), with slower increases thereafter as indicated.
- In less acutely ill outpatients, dose adjustments should be slower to minimize side effects.
- Maintenance dosages average about 1000 mg/day but may range from 200 to 1600 mg/day in routine clinical practice.
- Levels established for treatment of seizure disorders (serum concentration between 4 and 12 μg/mL) are generally applied to patients with bipolar disorder.
- Use trough levels (drawn prior to the first morning dose) 5 days after a dose change.

Implementation *(continued)*

Long-term monitoring of laboratory values

- CBC, platelet, and liver function tests should be performed every 2 weeks during the first 2 months of carbamazepine treatment.
- Thereafter, if laboratory tests remain normal and no symptoms of bone marrow suppression or hepatitis appear, blood counts and liver function tests should be obtained at least every 3 months; more frequent monitoring is necessary if there are hematological or hepatic abnormalities.

5. Antipsychotic Medications

Implementation and relative side effects of second-generation antipsychotic medications with FDA indications for treatment of acute manic or mixed episodes are described in Table 1 (p. 190).

TABLE 1. Dosing and Relative Side Effects of Second-Generation Antipsychotic Agents for the Treatment of Acute Mania or Mixed Episodes

Medication	Initial Dosing[a]	Typical Dose Range	Weight Gain, Glucose and Lipid Abnormalities	QTc Prolongation	Sedation and Hypotension	Anticholinergic Effects
Aripiprazole	30	10–30	0	0	0/+	0
Risperidone	3	2–8	++	+	+	0
Olanzapine	10–15	10–30	+++	0	+	++
Quetiapine	100	300–800	++	0	++	0
Ziprasidone	80	120–200	0	++	0	0

0 = No risk or rarely causes side effects at therapeutic dose. + = Mild or occasionally causes side effects at therapeutic dose. ++ = Sometimes causes side effects at therapeutic dose. +++ = Frequently causes side effects at therapeutic dose.

[a]Lower starting doses may be indicated for outpatients, elderly patients, or patients taking other medications with potential drug-drug interactions.