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Practice Guideline for the Treatment of Patients With Bipolar Disorder (Revision)

PART B: Background Information and Review of Available Evidence

V. REVIEW AND SYNTHESIS OF AVAILABLE EVIDENCE

A. Somatic Treatments of Acute Manic and Mixed Episodes

In general, the primary goal of treatment for patients experiencing a manic or mixed episode is symptom control to allow a return to normal levels of psychosocial functioning. The rapid control of symptoms such as agitation and aggression may be particularly important for the safety of the patient and others.

1. Lithium

Lithium has been used for the treatment of acute bipolar mania for over 50 years. Five studies have demonstrated that lithium is superior to placebo (176-180). Pooled data from these studies reveal that 87 (70%) of 124 patients displayed at least partial reduction of mania with lithium. However, the use of a crossover design in four of these trials (176-179), nonrandom assignment in two studies (177,178), and variations in diagnostic criteria and trial duration limit interpretation of the results of all but one trial (180). Nevertheless, in the only placebo-controlled, parallel-design trial in which lithium served as an active comparator to divalproex, lithium and divalproex exerted comparable efficacy (180). In active comparator trials, lithium displayed efficacy comparable to that of carbamazepine (181,182), risperidone (183), olanzapine (184), and chlorpromazine and other typical antipsychotics (185-190). Among active comparator trials, however, only three (185,186,189) were likely to be of sufficient size to detect possible differences in efficacy between treatments. Open studies (191-194) and randomized, active comparator-controlled studies (195-197) indicate that lithium is likely to be effective for treatment of pure or elated mania but is less often effective in the treatment of mixed states.

a) Side effects. Up to 75% of patients treated with lithium experience some side effects (41,198). These side effects vary in clinical significance; most are either minor or can be reduced or eliminated by lowering the lithium dose or changing the dosage schedule. For example, Schou (199) reported a 30% reduction in side effects among patients treated with an average lithium level of 0.68 meq/liter compared with those treated with an average level of 0.85 meq/liter. Side effects that appear to be related to peak serum levels (e.g., tremor that peaks 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.

Dose-related side effects of lithium include polyuria, polydipsia, weight gain, cognitive problems (e.g., dulling, impaired memory, poor concentration, confusion, mental slowness), tremor, sedation or lethargy, impaired coordination, gastrointestinal distress (e.g., nausea, vomiting, dyspepsia, diarrhea), hair loss, benign leukocytosis, acne, and edema (200). Side effects that persist despite dosage adjustment may be managed with other medications (e.g., b blockers for tremor; diuretics for polyuria, polydipsia, or edema; topical antibiotics or retinoic acid for acne). Gastrointestinal disturbances can be managed by administering lithium with meals or changing lithium preparations (especially to lithium citrate).

Lithium may cause benign ECG changes associated with repolarization. Less commonly, cardiac conduction abnormalities have been associated with lithium treatment. Anecdotal reports have linked lithium with other ECG changes, including the exacerbation

of existing arrhythmias and, less commonly, the development of new arrhythmias (201).

The most common renal effect of lithium is impaired concentrating capacity caused by reduced renal response to ADH, manifested as polyuria, polydipsia, or both (202,203). Although the polyuria associated with early lithium treatment may resolve, persistent polyuria (ranging from mild and well tolerated to severe nephrogenic diabetes insipidus) may occur. Polyuria can frequently be managed by changing to a once-daily bedtime dose. If the polyuria persists, management includes ensuring that fluid intake is adequate and that the lithium dose is as low as possible. If these measures do not ameliorate the problem, then concurrent administration of a thiazide diuretic (e.g., hydrochlorothiazide at a dose of 50 mg/day) may be helpful. The lithium dose will usually need to be decreased (typically by 50%) to account for the increased reabsorption induced by thiazides (198). In addition, potassium levels will need to be monitored, and potassium replacement may be necessary. Amiloride, a potassium-sparing diuretic, is reported to be effective in treating lithium-induced polyuria and polydipsia (203). Its advantages are that it does not alter lithium levels and does not cause potassium depletion. Amiloride may be started at 5 mg b.i.d. and may be increased to 10 mg b.i.d. as needed (204).

Hypothyroidism occurs in 5%-35% of patients treated with lithium. It occurs more frequently in women, tends to appear after 6-18 months of lithium treatment, and may be associated with rapid cycling (41,80,198,205). Lithium-induced hypothyroidism is not a contraindication to continuing lithium and is easily treated by the administration of levothyroxine (198,205). In addition to the other signs and symptoms of hypothyroidism, patients with bipolar disorder are at risk of developing depression or rapid cycling. If these symptoms occur in the presence of laboratory evidence of suboptimal thyroid functioning, then thyroid supplementation, discontinuation of lithium, or both should be considered (206-208). Hyperparathyroidism has also been noted with lithium treatment (209-211).

A small number of case reports have described exacerbation or first occurrences of psoriasis associated with lithium treatment (212). Some of these patients improved with appropriate dermatologic treatment or when the lithium dose was lowered. In some cases, however, lithium seemed to block the effects of dermatologic treatment, with psoriasis clearing only after lithium was discontinued. In addition, patients occasionally experience severe pustular acne that does not respond well to standard dermatologic treatments and only resolves once the lithium treatment is discontinued (212). This is in contrast to the more common mild to moderate acne that can occur with lithium treatment, which is usually responsive to standard treatments (198).

Approximately 10%-20% of patients receiving long-term lithium treatment (i.e., for more than 10 years) display morphological kidney changes-usually interstitial fibrosis, tubular atrophy, and sometimes glomerular sclerosis. These changes may be associated with impairment of water reabsorption but not with reduction in glomerular filtration rate or development of renal insufficiency (41,198,213-216). Although irreversible renal failure caused by lithium has not been unequivocally established, there are a number of case reports of probable lithium-induced renal insufficiency (215,217,218). Additionally, several studies have shown that a small percentage of patients treated with lithium may develop rising serum creatinine concentrations after 10 years or more of treatment (215,218).

b) Toxicity/overdose. Toxic effects of lithium become more likely as the serum level rises (219). Most patients will experience some toxic effects with levels above 1.5 meq/liter; levels above 2.0 meq/liter are commonly associated with life-threatening side effects. For many patients, the therapeutic range within which beneficial effects outweigh toxic effects is quite narrow, so that small changes in serum level may lead to clinically significant alterations in the beneficial and harmful effects of lithium. Elderly patients may experience toxic effects at lower levels and have a correspondingly narrower therapeutic window (138).

Signs and symptoms of early intoxication (with levels above 1.5 meq/liter) include marked tremor, nausea and diarrhea, blurred vision, vertigo, confusion, and increased deep tendon reflexes. With levels above 2.5 meq/liter, patients may experience more severe neurological complications and eventually experience seizures, coma, cardiac dysrhythmia, and permanent neurological impairment. The magnitude of the serum level and the duration of exposure to a high level of lithium are both correlated with risk of adverse effects (219). Therefore, rapid steps to reduce the serum level are essential. In addition, during treatment for severe intoxication, patients may experience "secondary peaks" during which the serum level rises after a period of relative decline; the clinician must therefore continue to monitor serum levels during treatment for severe intoxication. The patient with lithium intoxication should be treated with supportive care (e.g., maintenance of fluid and electrolyte balance), and steps should be taken to prevent further absorption of the medication (e.g., gastric lavage or, in the alert patient, induction of emesis).

Hemodialysis is the only reliable method of rapidly removing excess lithium from the body and is more effective than peritoneal dialysis for this purpose (220). Criteria for the use of hemodialysis in lithium intoxication are not firmly established, and the decision to dialyze must take into account both the patient's clinical status and the serum lithium level (219,221). When serum lithium levels are below 2.5 meq/liter, hemodialysis usually is unnecessary. The need for hemodialysis differs in patients who have developed toxicity after an acute overdose compared with those who have developed gradual toxicity or have an acute overdose superimposed on long-term lithium treatment. In acute poisoning, hemodialysis is generally required with serum lithium levels over 6-8 meq/liter, whereas hemodialysis may be needed with serum levels over 4 meq/liter in those who have been on long-term regimens of lithium treatment. Hemodialysis may also be necessary at lower serum levels in patients who are more susceptible to complications because of underlying illnesses (e.g., cardiac disease, renal impairment). Regardless of serum lithium level, hemodialysis is generally indicated in patients with progressive clinical deterioration or severe clinical signs of intoxication such as coma, convulsions, cardiovascular symptoms, or respiratory failure (219,221). Because serum levels of lithium may rebound after initial hemodialysis, repeat dialysis may be needed (219,222).

In cases of overdose with sustained-release preparations of lithium, development of toxicity is likely to be delayed, and the duration of toxicity is likely to be prolonged (223,224). This should be taken into consideration in decisions about the need for initial or repeat hemodialysis (219).

c) Implementation and dosing. Before beginning lithium treatment, the patient's general medical history should be reviewed, with special reference to those systems that might affect or be affected by lithium therapy (e.g., renal, thyroid, and cardiac functioning). In addition, pregnancy or the presence of a dermatologic disorder must be ascertained. Patient education should address potential side effects of lithium treatment as well as the need to avoid salt-restricted diets or concomitant medications that could elevate serum lithium levels (e.g., diuretics, angiotensin-converting enzyme inhibitors, nonsteroidal anti-inflammatory

drugs, cyclooxygenase-2 inhibitors). Patients should be cautioned, particularly if nephrogenic diabetes insipidus is present, that lithium toxicity might occur with dehydration from environmental heat, gastrointestinal disturbance, or inadequate fluid intake.

Laboratory measures and other diagnostic tests are generally recommended on the basis of pathophysiological knowledge and anticipated clinical decisions rather than on empirical evidence of their clinical utility. The decision to recommend a test is based on the probability of detecting a finding that would alter treatment as well as the expected benefit of such alterations in treatment. Recommended tests fall into three categories: 1) baseline measures to facilitate subsequent interpretation of laboratory tests (e.g., ECG, CBC); 2) tests to determine conditions requiring different or additional treatments (e.g., pregnancy, thyroid-stimulating hormone level); and 3) tests to determine conditions requiring alteration of the standard dosage regimen of lithium (e.g., creatinine level).

On the basis of these considerations, the following procedures are generally recommended before beginning lithium therapy: a general medical history, a physical examination, BUN and creatinine level measurement, a pregnancy test, thyroid function evaluation, and, for patients over age 40, ECG monitoring with rhythm strip. Some authorities also suggest a CBC.

Lithium is usually started in low, divided doses to minimize side effects (e.g., 300 mg t.i.d. or less, depending on the patient's weight and age), with the dose titrated upward (generally to serum concentrations of 0.5-1.2 meq/liter) according to response and side effects (225). Lithium levels should be checked after each dose increase and before the next. Steady-state levels are likely to be reached approximately 5 days after dose adjustment, but levels may need to be checked sooner if a rapid increase is necessary (e.g., in the treatment of acute mania) or if toxicity is suspected. As levels approach the upper limits of the therapeutic range (i.e., ³ 1.0 meq/liter), they should be checked at shorter intervals after each dose increase to minimize the risk of toxicity.

Serum concentrations required for prophylaxis may be, in some cases, as high as those required for treatment of the acute episode. A controlled study by Gelenberg et al. (225) found that patients randomly assigned to a "low" lithium level (0.4-0.6 meq/liter) had fewer side effects but more illness episodes than patients in the "standard" lithium group (0.8-1.0 meq/liter). However, the lithium levels of some of the patients in the low-lithium group decreased relatively rapidly from their previous treatment levels, a decrease that could have increased their risk of relapse. Although the prophylactic efficacy of lithium levels between 0.6 and 0.8 meq/liter has not been formally studied, this range is commonly chosen by patients and their psychiatrists (226). Despite the lack of formal study, it is likely that for many patients, increases in maintenance lithium levels will result in a trade-off between greater protection from illness episodes at the cost of an increase in side effects. The "optimal" maintenance level may therefore vary somewhat from patient to patient. Some patients find that a single, daily dose facilitates treatment compliance and reduces or does not change side effects.

The clinical status of patients receiving lithium needs to be monitored especially closely. The frequency of monitoring depends on the individual patient's clinical situation but generally should be no less than every 6 months for stable patients. The optimal frequency of serum level monitoring in an individual patient depends on the stability of lithium levels over time for that patient and the degree to which the patient can be relied upon to notice and report symptoms.

In general, renal function should be tested every 2-3 months during the first 6 months of treatment, and thyroid function should be evaluated once or twice during the first 6 months of lithium treatment. Subsequently, renal and thyroid function may be checked every 6 months to 1 year in stable patients or whenever clinically indicated (e.g., in the presence of breakthrough affective symptoms, changes in side effects, or new medical or psychiatric signs or symptoms) (198,214).

2. Divalproex/valproate/valproic acid

Divalproex and its sodium valproate and valproic acid formulations have been studied in four randomized, placebo-controlled trials: two small crossover trials (227,228) and two parallel-group trials (180,229). All four studies found significantly greater efficacy for valproate compared with placebo, with response rates ranging from 48% to 53%. Secondary analyses (150,197) of data from the largest parallel-group trial (180) suggested that patients with prominent depressive symptoms during mania and with multiple prior mood episodes were more likely to respond to acute treatment with divalproex than with lithium. An additional randomized comparison also reported valproate to be more efficacious than lithium among manic patients with mixed symptoms (195). In patients with acute mania, divalproex was comparable in efficacy to haloperidol in an open trial (230) and to olanzapine in a randomized, controlled trial (231) in the reduction of symptoms of mania and psychosis. In contrast, in a second head-to-head comparison trial (232), olanzapine was superior to divalproex in the mean reduction of manic symptoms and in the proportion of patients in remission at the end of the study.

a) Side effects. Minor side effects of valproate, such as sedation or gastrointestinal distress, are common initially and typically resolve with continued treatment or dose adjustment. In addition, valproate has a wide therapeutic window. Inadvertent overdose is uncommon, and purposeful overdose is less likely to be lethal than it is with lithium. However, in rare instances, valproate can cause life-threatening side effects, and patients must be relied upon to report the often subtle symptoms of these reactions promptly.

Common dose-related side effects of valproate include gastrointestinal distress (e.g., anorexia, nausea, dyspepsia, vomiting, diarrhea), benign hepatic transaminase elevations, osteoporosis (233,234), tremor, and sedation. Patients with past or current hepatic disease may be at greater risk for hepatotoxicity (235). Mild, asymptomatic leukopenia and thrombocytopenia occur less frequently and are reversible upon drug discontinuation. Other side effects that are often bothersome to the patient include hair loss (236,237), increased appetite, and weight gain. Persistent gastrointestinal distress associated with valproate can be alleviated by dose reduction, change of preparation (use of the divalproex sodium formulation rather than valproic acid), or by administration of a histamine-2 antagonist (e.g., famotidine or cimetidine) (238-242). Tremor can be managed with dose reduction or coadministration of β blockers. Cases of mild, asymptomatic leukopenia (total WBC count $>3000/\text{mm}^3$ and polymorphonuclear leukocyte count $<1500/\text{mm}^3$) are usually reversible upon dose reduction or discontinuation. Similarly, if mild, asymptomatic thrombocytopenia occurs, a decrease in valproate dose will usually restore the platelet count to normal. However, more severe cases of thrombocytopenia have been reported (243).

The relationship between polycystic ovarian syndrome and valproate treatment is unclear (244-246). One uncontrolled report indicated that 80% of women receiving long-term valproate treatment for epilepsy before the age of 20 had polycystic ovaries or hyperandrogenism (247). Other cross-sectional studies have demonstrated higher rates of polycystic ovaries and polycystic ovarian

syndrome in women with epilepsy (244-246). However, none of the studies examined whether the polycystic ovarian syndrome began before or after the development of epilepsy or the initiation of valproate therapy (246). Furthermore, women with bipolar disorder may differ from women with epilepsy in their rates of polycystic ovarian syndrome independent of treatment. An accurate assessment of risk will require a longitudinal study of women with bipolar disorder before and after initiation of valproate treatment (246). Consequently, although the risks are unclear, psychiatrists should be aware that polycystic ovarian syndrome may be possible with valproate treatment, and thus patients should be monitored accordingly (244).

Rare, idiosyncratic, but potentially fatal adverse events with valproate include irreversible hepatic failure, hemorrhagic pancreatitis, and agranulocytosis. Thus, patients taking valproate need to be instructed to contact their psychiatrist or primary care physician immediately if they develop symptoms of these conditions.

b) Toxicity/overdose. Valproate has a wide therapeutic window, so unintentional overdose is uncommon (248). Signs of overdose include somnolence, heart block, and eventually coma. Deaths have been reported. Overdose can be treated with hemodialysis (249,250).

c) Implementation and dosing. Before initiating valproate treatment, a general medical history should be taken, with special attention to hepatic, hematologic, and bleeding abnormalities. Results of liver function tests and hematologic measures should be obtained at baseline to evaluate general medical health.

Data from a number of open trials (230,251-253) and one randomized controlled trial (254) indicate that divalproex can be administered at a therapeutic initial starting dose of 20-30 ug/kg per day in inpatients. This strategy appears to be well tolerated and may be more rapidly efficacious than more gradual titration from a lower starting dose (254). After a serum valproate level is obtained, the dose is then adjusted downward to achieve a target level between 50 and 125 µg/ml.

Among outpatients, elderly patients, or patients who are hypomanic or euthymic, valproate may be initiated in low, divided doses to minimize gastrointestinal and neurological toxicity. Valproate should generally be started at 250 mg t.i.d., with the dose increased every few days as side effects allow (204). Depending upon clinical response and side effects, the dose is then titrated upward by 250- 500 mg/day every few days, generally to a serum concentration of 50-125 µg/ml, with a maximum adult daily dose of 60 mg/kg per day (250). Once the patient is stable, valproate regimens can be simplified to enhance convenience and compliance, since many patients do well with once- or twice-a-day dosing.

Extended-release divalproex, a new formulation that allows for once-a-day dosing, has become available. Bio-availability is approximately 15% lower than the immediate-release formulation (hence usually requiring slightly higher doses), and side effect profiles appear to be better than that of the immediate-release formulation (255). Demonstration of efficacy in patients with bipolar disorder is limited to open studies (255-257).

Asymptomatic hepatic enzyme elevations, leukopenia, and thrombocytopenia do not reliably predict life-threatening hepatic or bone marrow failure. In conjunction with careful monitoring of clinical status, educating patients about the signs and symptoms of hepatic and hematologic dysfunction and instructing them to report these symptoms if they occur are essential. Some investigators believe that in otherwise healthy patients with epilepsy receiving long-term valproate treatment, routine monitoring of hematologic and hepatic function is not necessary (258). Nevertheless, most psychiatrists perform clinical assessments, including tests of hematologic and hepatic function, at a minimum of every 6 months for stable patients who are taking valproate (252,259,260). Patients who cannot reliably report signs or symptoms of toxicity need to be monitored more frequently.

Psychiatrists should be alert to the potential for interactions between valproate and other medications (261). For example, valproate displaces highly protein-bound drugs from their protein binding sites. In addition, valproate inhibits lamotrigine metabolism and more than doubles its elimination half-life by competing for glucuronidation enzyme sites in the liver (262,263). Consequently, in patients treated with valproate, lamotrigine must be initiated at a dose that is less than half that used in patients who are not receiving concomitant valproate.

3. Carbamazepine

Many controlled trials of carbamazepine have been conducted in the treatment of acute bipolar mania, but interpretation of the results of a number of these studies is difficult because of the confounding effects of other medications administered as part of study protocols (264). Carbamazepine was superior to placebo in one randomized, crossover trial (265). Carbamazepine was less effective and associated with more need for adjunctive "rescue medication" than valproate in a randomized, blind, parallel-group trial of 30 hospitalized manic patients (266). Carbamazepine was comparable to lithium in two randomized comparison trials (181,182) and comparable to chlorpromazine in two other randomized trials (267,268).

a) Side effects. Up to 50% of patients receiving carbamazepine experience side effects, and the drug is associated with potentially serious adverse reactions (258,269,270).

The most common dose-related side effects of carbamazepine include neurological symptoms, such as diplopia, blurred vision, fatigue, nausea, and ataxia. These effects are usually transient and often reversible with dose reduction. Elderly patients, however, may be more sensitive to side effects. Less frequent side effects include skin rashes (271), mild leukopenia, mild thrombocytopenia, hyponatremia, and (less commonly) hypo-osmolality. Mild liver enzyme elevations occur in 5%-15% of patients. Mild asymptomatic leukopenia is not related to serious idiopathic blood dyscrasias and usually resolves spontaneously with continuation of carbamazepine treatment or with dose reduction. In the event of asymptomatic leukopenia, thrombocytopenia, or elevated liver enzymes, the carbamazepine dose can be reduced or, in the case of severe changes, discontinued. Hyponatremia may be related to water retention caused by carbamazepine's antidiuretic effect (272). Hyponatremia occurs in 6%-31% of patients, is rare in children but probably more common in the elderly, occasionally develops many months after the initiation of carbamazepine treatment, and sometimes necessitates carbamazepine discontinuation. In addition, carbamazepine may decrease total and free thyroxine levels and increase free cortisol levels, but these effects are rarely clinically significant. Weight gain is also a common side effect of carbamazepine.

Rare, idiosyncratic, but serious and potentially fatal side effects of carbamazepine include agranulocytosis, aplastic anemia,

thrombocytopenia, hepatic failure, exfoliative dermatitis (e.g., Stevens-Johnson syndrome), and pancreatitis (243,258,273-275). Although these side effects usually occur within 3-6 months of carbamazepine initiation, they have also occurred after more extended periods of treatment. Routine blood monitoring does not reliably predict blood dyscrasias, hepatic failure, or exfoliative dermatitis. Thus, in addition to careful monitoring of clinical status, it is essential to educate patients about the signs and symptoms of hepatic, hematologic, or dermatologic 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).

b) Toxicity/overdose. Carbamazepine may be fatal in overdose; deaths have been reported with ingestions of more than 6 g. Signs of impending carbamazepine toxicity include dizziness, ataxia, sedation, and diplopia. Acute intoxication can result in hyperirritability, stupor, or coma. The most common symptoms of carbamazepine overdose are nystagmus, ophthalmoplegia, cerebellar and extrapyramidal signs, impaired consciousness, convulsions, and respiratory dysfunction. Cardiac symptoms may include tachycardia, arrhythmia, conduction disturbances, and hypotension. Gastrointestinal and anticholinergic symptoms may also occur. Management of carbamazepine intoxication includes symptomatic treatment, gastric lavage, and hemoperfusion.

c) Implementation and dosing. A pretreatment evaluation for carbamazepine should include a general medical history and physical examination, with special emphasis on prior history of blood dyscrasias or liver disease. Most authorities recommend that the minimum baseline evaluation include a CBC with differential and platelet count, a liver profile (evaluation of LDH, SGOT, SGPT, bilirubin, and alkaline phosphatase), and renal function tests (204). Serum electrolyte levels may also be obtained, especially in the elderly, who may be at higher risk for hyponatremia.

Although doses can range from 200 to 1800 mg/day, the relationships among dose, serum concentration, response, and side effects are variable. Therefore, the dose should be titrated upward according to response and side effects. In patients over the age of 12, carbamazepine is usually begun at a total daily dose of 200-600 mg, given in three to four divided doses. In hospitalized patients with acute mania, the dose may be increased in increments of 200 mg/day up to 800-1000 mg/day (unless side effects develop), with slower increases thereafter as indicated. In less acutely ill outpatients, dose adjustments should be slower, since rapid increases may cause patients to develop nausea and vomiting or mild neurological symptoms such as drowsiness, dizziness, ataxia, clumsiness, or diplopia. Should such side effects occur, the dose can be decreased temporarily and then increased again more slowly once these side effects have passed.

While therapeutic serum levels of carbamazepine have not been established for patients with bipolar disorder, serum concentrations established for treatment of seizure disorders (4-12 µg/ml) are generally applied. Trough levels are most meaningful for establishing an effective level for a given patient and are conveniently drawn before the first morning dose. Serum levels should be determined 5 days after a dose change or sooner if toxicity or noncompliance is suspected. Maintenance doses average about 1000 mg/day but may range from 200-1600 mg/day in routine clinical practice (204). Doses higher than 1600 mg/day are not recommended.

CBCs, platelet measurements, and liver function tests should be performed every 2 weeks during the first 2 months of carbamazepine treatment. Thereafter, if results of laboratory tests remain normal and no symptoms of bone marrow suppression or hepatitis appear, blood counts and liver function tests should be performed at least every 3 months (204). More frequent monitoring is necessary in patients with laboratory findings, signs, or symptoms consistent with hematologic or hepatic abnormalities. Life-threatening reactions, however, are not always detected by routine monitoring. The psychiatrist should educate patients about signs and symptoms of hepatic, hematologic, or dermatologic reactions and instruct patients to report these symptoms if they occur. More frequent clinical and laboratory assessments are needed for those patients who cannot reliably report symptoms.

Psychiatrists should be aware that carbamazepine is able to induce drug metabolism, including its own, through cytochrome P-450 oxidation and conjugation (261,263,276). This enzymatic induction may decrease levels of concomitantly administered medications such as valproate, lamotrigine, oral contraceptives, protease inhibitors, benzodiazepines, and many antipsychotic and antidepressant medications. In addition, carbamazepine has an active epoxide metabolite and is metabolized primarily through a single enzyme, cytochrome P-450 isoenzyme 3A3/4, making drug-drug interactions even more likely. Consequently, carbamazepine levels may be increased by medications that inhibit the cytochrome P-450 isoenzyme 3A3/4, such as fluoxetine, fluvoxamine, cimetidine, and some antibiotics and calcium channel blockers.

Thus, in patients treated with carbamazepine, more frequent clinical and laboratory assessments may be needed with addition or dose adjustments of other medications.

4. Other anticonvulsants

Oxcarbazepine, the 10-keto analog of carbamazepine, was comparable in efficacy to lithium and haloperidol in two small trials (277,278). However, these studies lacked sufficient power to detect possible drug-drug differences. While direct comparisons with carbamazepine in studies of bipolar disorder are lacking, studies of epilepsy suggest that oxcarbazepine may have a lower rate of severe side effects (279) and be well tolerated overall (280), although it has been associated with clinically significant hyponatremia (281). Moreover, unlike carbamazepine, oxcarbazepine does not induce its own metabolism (282). However, it may still decrease plasma concentrations of oral contraceptives and dihydropyridine calcium channel blockers, requiring medication change or dose adjustment. (For a more complete review, see the bipolar disorder treatment algorithm of the Texas Medication Algorithm Project [283].)

Three controlled studies, all with methodological limitations, have evaluated lamotrigine in the treatment of bipolar mania. In the first trial, 28 patients with bipolar I or bipolar II disorder were assessed in a double-blind, randomized, crossover series of three 6-week monotherapy trials of lamotrigine, gabapentin, or placebo (284). The response rate for manic symptom improvement, as measured by the Clinical Global Impression Scale for Bipolar Illness, did not differ significantly among the three treatment groups. However, the low mean Young Mania Rating Scale scores at baseline, the crossover design, and the small number of subjects may have limited the findings. In the second study, 16 outpatients with mania, hypomania, or mixed episodes who were inadequately responsive to or unable to tolerate lithium were randomly assigned to lamotrigine or placebo as mono- or adjunctive therapy (285). There were no significant differences between lamotrigine and placebo groups on changes in Young Mania Rating Scale scores or response rates. Limitations of this study included the small study group size and high (50%) placebo response rate. In

the third study, 30 inpatients were randomly assigned to lamotrigine or lithium for 4 weeks (286). Both treatment groups displayed significant and comparable reductions in manic symptoms from baseline to end-point. Limitations of this study included lack of a placebo group, small patient group size, and use of relatively low lithium levels (mean plasma concentration of 0.7 meq/liter at study endpoint). Adverse events and implementation and dosing issues associated with lamotrigine treatment are described in detail in section V.B.2.c. (p. 27).

Two controlled studies have evaluated the efficacy of gabapentin in the treatment of bipolar manic symptoms. In the first study (284), there were no significant differences in efficacy between gabapentin monotherapy and placebo in improvement in manic symptoms. The second controlled trial (287) compared gabapentin with placebo added to lithium, valproate, or both in 114 outpatients with manic, hypomanic, or mixed symptoms. Both treatment groups displayed a decrease in Young Mania Rating Scale scores from baseline to endpoint, but this decrease was significantly greater in the placebo group.

Finally, one small placebo-controlled trial also suggested efficacy for the anticonvulsant phenytoin in the treatment of mania when added to haloperidol treatment (288).

5. Olanzapine

Olanzapine was superior to placebo in the treatment of acute bipolar mania in two large, multicenter randomized controlled trials. In the first trial (289), olanzapine versus placebo differences did not reach statistical significance until the third week of treatment. In the second study (290), significant reductions in manic symptoms were apparent in olanzapine-treated patients compared with those receiving placebo at the first assessment point (after 1 week). These differences were probably due to differences in initial starting dose, since the initial olanzapine dose was 10 mg/day in the first study and 15 mg/day in the second trial. In a secondary analysis of data from the second trial, in which sufficient proportions of patients with mixed episodes or rapid cycling were included for comparison, olanzapine response was comparable in patients with or without these features (291). In other randomized, controlled trials, olanzapine exerted comparable efficacy to lithium (184), divalproex (231), and haloperidol (292) in the reduction of manic symptoms. Olanzapine was superior to divalproex in a randomized comparison trial (232). Last, olanzapine was superior to placebo as adjunctive therapy to lithium or divalproex in a randomized, controlled acute treatment trial (292).

a) Side effects. In short-term, placebo-controlled clinical trials, somnolence was the most common side effect associated with olanzapine. Other common side effects included constipation, dry mouth, increased appetite, and weight gain (291). Especially during initial dose titration, olanzapine may induce orthostatic hypotension associated with dizziness, tachycardia, and, in some patients, syncope. Syncope was reported in 0.6% of olanzapine-treated patients in phase II and III trials.

In clinical trials, seizures occurred in 0.9% of olanzapine-treated patients. Although confounding factors may have contributed to seizures in many instances, olanzapine should be used cautiously in patients with a history of seizure disorder or in clinical conditions associated with lowered seizure threshold. Transient elevations in plasma prolactin concentrations were also observed in short-term trials (293). These elevations typically remained within the normal physiological range and decreased with continued treatment. Clinically significant hepatic transaminase elevations

(≥ 3 times the upper limit of the normal range) were observed in 2% of olanzapine-treated patients.

In long-term studies, 56% of olanzapine-treated patients gained $>7\%$ of their baseline weight. In retrospective analyses of patients followed for a median of 2.54 years, the mean and median weight gains were 6.26 kg and 5.9 kg, respectively (294). Weight gain did not appear to be dose related, occurred most rapidly within the first 39 weeks of treatment, was greatest in patients with the lowest baseline body mass index, and was not correlated with increases in serum glucose. Increases in serum glucose in olanzapine-treated patients did not differ significantly from those in patients treated with haloperidol (294). Weight gain and hyperglycemia in patients treated with atypical antipsychotics have been reviewed in detail elsewhere (295,296).

In short-term trials, there were no significant differences in the incidence of dystonic reactions, parkinsonism, akathisia, or dyskinesic events among patients receiving placebo or olanzapine (291). Also, extrapyramidal side effects with olanzapine were substantially less than those seen with conventional antipsychotic medications such as haloperidol (297). In a 1-year haloperidol-controlled trial, the incidence of dyskinesic movements among olanzapine-treated patients with schizophrenia was 0.6% compared with 7.5% in patients receiving haloperidol (298). This incidence rate is confounded by prior treatment with typical antipsychotics and the rate of spontaneous dyskinesia in patients with schizophrenia. In 98 patients with bipolar disorder who received olanzapine for 1 year, some in combination with lithium or fluoxetine, no patients developed dyskinesic movements (291).

b) Implementation and dosing. In the two placebo-controlled studies of olanzapine in patients with bipolar mania, the mean final dose was approximately 15 mg/day. In the first study in which olanzapine was initiated at 10 mg/day and then titrated according to response and side effects, olanzapine did not differentiate from placebo until the third week of the trial (289). The second trial used a starting dose of 15 mg/day and found a significant difference in efficacy in favor of olanzapine at 1 week (the time of the first rating) (290). Taken together, the results of these trials suggest that for inpatients with acute mania, a start-ing dose of 15 mg/day may be more rapidly efficacious. For outpatients, lower starting doses of 5-10 mg/day may be indicated (299).

6. Other antipsychotics

Only one randomized, placebo-controlled study of typical antipsychotic medications has been reported in the treatment of acute bipolar mania (300). In this study, chlorpromazine was superior to placebo in global improvement of manic symptoms. Typical antipsychotics were comparable to lithium in reducing manic and psychotic symptoms in acute treatment comparison trials (185-190).

Among the atypical antipsychotic agents, risperidone and ziprasidone have also been studied in the treatment of acute bipolar mania with randomized, placebo-controlled trials. As an adjunct to treatment with lithium or divalproex, risperidone was comparable to haloperidol and superior to placebo (301). Ziprasidone was also superior to placebo in a large, multicenter monotherapy trial, with significant differences in favor of ziprasidone apparent at the time of the first rating, day 2 of treatment (302). While no placebo-controlled trials exist for the use of clozapine in the treatment of bipolar disorder, one randomized 1-year trial in patients with refractory bipolar or schizoaffective disorder showed greater clinical improvement with the addition of clozapine than with treatment as usual (303). An open trial of clozapine in the treatment of refractory mania was also associated with improvement in manic symptoms (304,305). In general, these trials have used dose ranges similar to those used in schizophrenia trials, with similar rates of adverse events.

7. Combination therapy

Controlled trials of lithium plus an antipsychotic and of valproate plus an antipsychotic suggest greater efficacy or more rapid onset of action with these combinations than with any of these agents alone. All of these studies involved patients who were currently being treated but who experienced breakthrough episodes of mania or incomplete response to monotherapy. The studies compared combination therapies: an antipsychotic combined with either valproate or placebo (306); lithium or valproate combined with either olanzapine or placebo (290); lithium or valproate combined with either risperidone or placebo (301); or lithium, valproate, or carbamazepine combined with either risperidone or placebo (307). This last trial supported combination therapy only when the carbamazepine-treated group was excluded.

8. ECT

Three prospective studies have assessed clinical outcomes of treatment of acute mania with ECT. In a prospective, randomized controlled trial (308), patients who received ECT followed by lithium maintenance treatment exhibited greater improvement after 8 weeks than did patients who received lithium as both acute and maintenance treatment. Clinical outcomes with ECT were also found to be superior to outcomes with a combination of lithium and haloperidol (309). In a third study (310), 30 manic patients were all treated with chlorpromazine but were randomly assigned to receive a course of either six ECT sessions or six sham ECT sessions. Patients treated with sham ECT did significantly worse than those treated with real ECT. Although all of these studies had small study group sizes, the results were consistent with other earlier retrospective comparisons of outcome in mania (311,312) and with earlier naturalistic case series (see Mukherjee et al. [309] and the APA Task Force Report on ECT [110] for reviews).

Although there are no prospective, randomized controlled studies of the use of ECT in the treatment of mixed states, in the aforementioned trial of ECT for treatment of mania (308), the strongest predictor of clinical response was the baseline rating of depressive symptoms. Case reports also suggest that ECT may be efficacious in treatment of mixed states (313-315).

Information on side effects and implementation of ECT can be found in the APA Task Force Report on ECT (110).

9. Novel treatments

A number of new agents are under active investigation as potential treatments for patients with acute bipolar mania, but data regarding their efficacy from randomized controlled trials are not yet available. These agents include the atypical antipsychotics quetiapine and aripiprazole; the antiepileptics zonisamide, acamprosate, and levetiracetam; and omega-3 fatty acids (316).

Two other medication classes, benzodiazepines and calcium channel blockers, have been studied in randomized controlled trials for treatment of acute bipolar mania. Among the benzodiazepines, clonazepam and lorazepam have been studied alone and in combination with lithium (317-322). Interpretation of many of these studies is confounded by small study group sizes, short treatment durations, concomitant antipsychotic use, and difficulties in distinguishing putative antimanic effects from nonspecific sedative effects. Taken together, however, these studies suggest that the sedative effects of benzodiazepines may make them effective treatment adjuncts while awaiting the effects of a primary antimanic agent to become evident. The fact that lorazepam, unlike other benzodiazepines, is well absorbed after intramuscular injection has made it particularly useful for the management of agitation. However, intramuscular olanzapine was superior to intramuscular lorazepam in ameliorating agitation in patients with bipolar mania (322).

Two randomized, controlled trials found little support for the efficacy of the calcium channel antagonist verapamil in the treatment of acute mania. In the first study, verapamil was compared with lithium in 40 patients hospitalized for an acute manic episode (323). The mean reduction in manic symptoms was significantly greater in the group of patients receiving lithium compared with the verapamil-treated group. The second trial, a 3-week double-blind study involving 32 patients with acute mania (324), showed no significant differences in efficacy between verapamil and placebo. These studies indicate that lithium was superior to verapamil and that verapamil, in turn, was not superior to placebo as an antimanic agent. In contrast, in a crossover trial involving 12 patients with refractory ultrarapid-cycling bipolar disorder (325), the calcium channel antagonist nimodipine was superior to placebo in ameliorating mood cycling.

B. Somatic Treatments of Acute Depressive Episodes

Somatic treatments that have been studied in bipolar depression include lithium, anticonvulsants, antidepressants, and ECT. Open studies and case reports comprise most of the literature on the treatment of bipolar depression, with the best-controlled data relating to treatment with lithium, lamotrigine, and paroxetine.

In general, the goals for treatment of acute depression in a patient with bipolar disorder are identical to those for patients with nonbipolar depression. The primary goal is remission of the symptoms of major depression and a return to normal levels of psychosocial functioning. Concerns about precipitation of a manic or hypomanic episode introduce management issues in the treatment of bipolar depression that do not exist for unipolar depression. This section will present efficacy data on lithium, anticonvulsants, antidepressants, ECT, and novel treatments. Information on side effects and implementation and dosing issues for lithium and the anticonvulsants are presented in this guideline in their respective sections under "Somatic Treatments of Acute Manic and Mixed Episodes" (section V.A.). Information on side effects and implementation and dosing issues for the antidepressants is provided in the *APA Practice Guideline for the Treatment of Patients With Major Depressive Disorder* (2).

1. Lithium

There have been eight placebo-controlled studies of lithium in the treatment of bipolar depression that had five or more subjects. All of these studies employed crossover designs, and all were completed before 1980 (for a review, see Zornberg and Pope [326]). Among a total of 160 patients, the overall rate of response to lithium, regardless of the degree of improvement or relapse with placebo, was 79%. However, the "unequivocal" lithium response rate, defined as a good or moderate response to lithium with a subsequent relapse when given placebo, was much lower (36%). An additional consideration in the use of lithium as an antidepressant is its time to onset (6-8 weeks), which is later than its antimanic effect (326).

2. Anticonvulsants

a) Divalproex and sodium valproate. There have been no published controlled studies of valproate in the treatment of bipolar depression. In an unpublished study, 43 subjects with bipolar I or bipolar II depression were entered into an 8-week, double-blind, placebo-controlled trial of divalproex. Forty-three percent of divalproex-treated patients and 27% of placebo-treated patients achieved recovery, defined as an improvement of $\geq 50\%$ in score on the 16-item Hamilton Depression Rating Scale in the absence of hypomania (Young Mania Rating Scale score < 10). This difference was not statistically significant (Gary Sachs and Michelle Collins, personal communication). While these results suggest that divalproex may be useful in the treatment of bipolar depression, a more definitive study is needed.

b) Carbamazepine. In a double-blind, placebo-controlled crossover study (327), four of nine patients with bipolar depression showed significant improvement from baseline in depressive symptoms with carbamazepine treatment.

In an open study of carbamazepine (328), there were significant reductions from baseline in 17-item Hamilton depression scale scores among 27 patients with bipolar depression and nine patients with mixed episodes. Patients with mixed episodes were significantly less likely to have a remission than those with bipolar depression.

c) Lamotrigine. Lamotrigine at doses of 50 mg/day and 200 mg/day was compared with placebo in a 7-week double-blind trial in 195 patients with bipolar I disorder with major depression (329). Both lamotrigine groups reported significantly better response rates on the Montgomery-Åsberg Depression Rating Scale but not on the Hamilton depression scale. The first significant lamotrigine versus placebo difference in Hamilton depression scale scores occurred at week 5 in the patients receiving 200 mg/day, whereas it occurred at week 7 in those given 50 mg/day. Switches into manic or hypomanic episodes occurred at equivalent rates (3%-8%) among the three groups.

In a flexible-dose, placebo-controlled study of lamotrigine in 206 patients with bipolar I or bipolar II major depression (330), both treatment groups improved significantly (response rate to lamotrigine was 50%, response rate to placebo was 49%), but lamotrigine did not distinguish itself from placebo. Lamotrigine was started at 25 mg/day and titrated over 5-6 weeks to the target dose of 400 mg/day. In a subgroup analysis, the patients with bipolar I disorder given lamotrigine did respond significantly better than those given placebo in terms of Montgomery-Åsberg Depression Rating Scale score (mean change of 13.5 versus 10.1, respectively).

In a double-blind, crossover study of patients with refractory, rapid-cycling bipolar I or bipolar II disorder who were treated with lamotrigine, gabapentin, or placebo, 45% of the depressed patients responded to lamotrigine, compared with response rates of 26% for gabapentin and 19% for placebo (284).

Finally, in an open study of patients with refractory bipolar disorder, 48% of 40 depressed patients treated with lamotrigine showed a marked response, and 20% showed a moderate response (331).

The most common side effects of lamotrigine in the treatment of depression are headache, nausea, infection, and xerostomia (39,329). However, none of these occurred at significantly higher percentage than with placebo (332).

The risk of serious rash, including Stevens-Johnson syndrome and toxic epidermal necrolysis, was found to be higher in patients treated for epilepsy in the first year after the introduction of lamotrigine in Europe (333). In clinical trials for epilepsy, the incidence of serious rash was approximately 0.3% in adults and approximately 1% in children (334,335). However, with a slow titration schedule, the risk of serious rash was reduced to 0.01% in adults (329), which is comparable to that of other anticonvulsant medications. Rash can occur at any time during treatment but is more likely to occur early in treatment. It may also be more likely if lamotrigine and valproate are administered concomitantly (334,335). Whenever lamotrigine is prescribed, patients should be apprised of the risk of rash and urged to contact the psychiatrist or primary care physician immediately if a rash occurs. At rash onset, it is difficult to distinguish between a serious and a more benign rash. Particularly worrisome 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 concurrent valproate) should be discontinued.

Lamotrigine should be administered at 25 mg/day for the first 2 weeks, then 50 mg/day for weeks 3 and 4. After that, 50 mg can be added per week as clinically indicated. With concurrent valproate treatment, pharmacokinetic interactions lead to lamotrigine levels that are approximately twice normal. To minimize the risk of potentially serious rash in patients who are receiving valproate, the dose schedule should be cut in half (i.e., 12.5 mg/day or 25 mg every other day for 2 weeks, then 25 mg/day for weeks 3 and 4). Similarly, concurrent carbamazepine treatment leads to an increase in lamotrigine metabolism and requires dosing to be doubled. Further details of lamotrigine dosing and adverse effects can be found in several reviews (262,334-337).

d) Topiramate. There are no placebo-controlled trials of topiramate in the treatment of bipolar depression, but several trials have suggested its efficacy as an add-on therapy. McIntyre et al. (338) conducted a single-blind, add-on study of topiramate and sustained-release bupropion in depressed patients with bipolar I or bipolar II disorder. Both groups had significant baseline-to-endpoint reduction in 17-item Hamilton depression scale and Clinical Global Impression (CGI) improvement scores, with no difference between the two groups. Thirty-three percent of patients receiving cotreatment with topiramate discontinued treatment because of adverse events compared with 22% of the patients receiving bupropion alone. The most common adverse events were sweating, blurred vision, difficulty sleeping, tremors, and paresthesia.

Hussain (339) conducted an open-label, add-on, 6-month study with topiramate in depressed patients with bipolar I or bipolar II disorder. Of 45 patients, 19 fully responded (Hamilton depression scale score=3-7), and 12 partially responded (Hamilton depression scale score=8-12). Five patients discontinued treatment because of lack of efficacy, and nine discontinued because of adverse events.

Conversely, in an open study of patients with bipolar I or bipolar II disorder, the 11 patients who were initially depressed and received add-on topiramate treatment had no significant improvements in either CGI or Inventory of Depressive Symptomatology scores (316).

3. MAOI antidepressants

a) Tranylcypromine. The efficacy of tranylcypromine was compared with that of imipramine in 56 outpatients with bipolar I or bipolar II depression (340). Compared with imipramine (at doses of at least 150 mg/day), tranylcypromine (at doses of at least 30 mg/day) produced significantly superior outcomes in terms of lower attrition, greater symptomatic improvement, and higher global response without a greater risk of treatment-emergent hypomania or mania.

In a second study (341), tranylcypromine was compared with imipramine in a double-blind crossover fashion for the 16 nonresponsive patients with bipolar I or bipolar II disorder from the previous trial. Tranylcypromine had comparatively better results, including lower attrition, greater symptomatic improvement, higher global response, and no greater risk of precipitating a switch into hypomania or mania.

b) Moclobemide. Moclobemide was compared to imipramine in a 4-week, multicenter, randomized study of 381 patients (342). No significant differences in efficacy were observed between the groups (both had response rates of 58%). The number of patients with adverse events and the total number of adverse events were greater in the imipramine group.

4. SSRIs and other newer antidepressant agents

a) Fluoxetine. Fluoxetine was compared with imipramine and placebo in 89 patients with bipolar depression. Twenty-two of the 89 patients were also taking lithium during the study. Eighty-six percent of the patients receiving fluoxetine over 6 weeks improved compared with 57% receiving imipramine and 38% given placebo. The response rate with fluoxetine was significantly better than that of both imipramine ($p < 0.05$) and placebo ($p = 0.005$). There were significantly fewer fluoxetine patients who discontinued treatment because of adverse events (343).

b) Paroxetine. Paroxetine was studied as an add-on treatment in three double-blind studies of patients with bipolar depression. In one study (344), depressed patients with bipolar I or bipolar II disorder maintained on regimens of lithium or divalproex were randomly assigned either to addition of paroxetine or a combination of lithium and divalproex in a 6-week outpatient trial. In terms of improvement from baseline in 17-item Hamilton depression scale scores, both treatments were equally effective at week 6: the mean scores of 6 and 9 in the subjects given lithium plus divalproex and those treated with adjunctive paroxetine, respectively, represented a decrease of 50%-70% ($p < 0.001$). There were more dropouts among those treated with the combination of lithium and divalproex.

In a placebo-controlled multicenter trial of paroxetine and imipramine in the treatment of patients with bipolar I depression maintained on a regimen of lithium (345), imipramine and paroxetine were found to be superior to placebo in patients whose serum lithium level was ≤ 0.8 meq/liter. In those patients with serum lithium levels > 0.8 meq/liter, there were no differences among the groups. Of the patients receiving imipramine, treatment-induced switches into manic or hypomanic episodes occurred in 6% of those with lithium levels > 0.8 meq/liter and 11% of those with lithium levels ≤ 0.8 meq/liter. Switches occurred in none of the paroxetine-treated patients and in 2% of the placebo group (all of whom had lithium levels ≤ 0.8 meq/liter).

Paroxetine and venlafaxine were studied in the treatment of patients with bipolar depression on a maintenance medication regimen (346). Forty-three percent of the paroxetine group and 48% of the venlafaxine group were rated as having responded (difference not significant). Whereas switches to episodes of mania or hypomania occurred in 3% of those treated with paroxetine, the rate of switching in the venlafaxine group was 13%.

c) Citalopram. In a 24-week, open-label trial, the use of citalopram as an add-on treatment was studied in 45 patients with bipolar depression (30 [67%] with bipolar I disorder) who were receiving lithium, valproate, or carbamazepine (347). Of the 33 patients who completed the 8-week acute phase, 64% responded, and most of these patients continued to improve through the 16-week continuation phase.

d) Bupropion. There have been two controlled studies of bupropion in the treatment of bipolar depression. In a double-blind, 8-week study (348), patients who had been maintained on regimens of lithium, valproate, or carbamazepine were randomly assigned to bupropion or desipramine treatment. The response rate was 55% for bupropion and 50% for desipramine, a nonsignificant difference. In the first 8 weeks, 30% of the patients receiving desipramine switched into a manic episode, whereas 11% of those receiving bupropion did. Over the entire study, with follow-up to 1 year, the observed rate of switching into manic or hypomanic episodes in patients receiving desipramine was 50%, whereas the rate was 11% with bupropion.

In a 6-week, double-blind study of bupropion versus idazoxan (a selective α -2 antagonist) in 16 patients with bipolar I disorder-some of whom were also on a maintenance regimen of lithium-no significant differences were seen between the groups (349).

e) Venlafaxine. In addition to the aforementioned double-blind study that compared venlafaxine with paroxetine (346), another study reported on 15 depressed women with bipolar II disorder who were treated with venlafaxine (350). Sixty-three percent of the patients experienced a $\geq 50\%$ reduction from baseline in scores on the 21-item Hamilton depression scale. Two patients (13%) discontinued treatment because of adverse events.

5. Tricyclic antidepressants

Imipramine and desipramine have been used as active control treatments in studies of tranylcypromine, fluoxetine, paroxetine, and bupropion. In general, the tricyclic antidepressants had response rates that were equivalent to or poorer than that of the active comparator (yet superior to placebo). In addition, treatment with tricyclic antidepressants was associated with higher rates of switching into manic or hypomanic episodes.

6. Antipsychotics

In an 8-week, double-blind study of olanzapine mono-therapy, olanzapine and fluoxetine combination therapy, and placebo in the treatment of 833 patients with acute bipolar I depression, olanzapine monotherapy and combination therapy were both significantly

better than placebo at endpoint (M. Tohen, personal communication, 2001). Furthermore, both of these treatment regimens showed significant separation from placebo at week 1.

7. ECT

Several controlled studies of ECT in patients with bipolar depression were conducted several decades ago (326). All found ECT to be as or more effective than MAOIs, tricyclic antidepressants, or placebo. ECT is a viable option for patients with severe bipolar depression, especially if psychotic features are present (110). For information on side effects and implementation of ECT, see the APA Task Force Report on ECT (110).

8. Novel treatments

Several studies have suggested that sleep deprivation has an antidepressant effect in patients with bipolar depression, although its effect is usually short-lived (351). It has been studied in conjunction with pindolol in a placebo-controlled protocol (352). Forty patients with bipolar depression were randomly assigned to receive either pindolol or placebo in combination with total sleep deprivation. Fourteen of 20 patients who underwent total sleep deprivation while receiving pindolol were rated as having responded (Hamilton depression scale score <8), whereas only one patient receiving placebo and pindolol responded. No switches into manic episodes were observed. Another study examined the value of phototherapy or lithium in conjunction with total sleep deprivation among 115 patients with bipolar depression (353). The authors reported that each adjunctive treatment improved total sleep-deprivation response rates, but the combination of all three added nothing.

Thyroid hormones, particularly thyroxine (T_4), have been reported to be useful in the treatment of bipolar disorder, particularly rapid cycling (205). In patients with nonbipolar depression, triiodothyronine (T_3) augmentation is associated with an antidepressant effect. The use of thyroid hormones in patients with bipolar depression remains to be studied.

The use of other agents, such as risperidone, olanzapine, ziprasidone, omega-3 fatty acids (354), pramipexole (355), or interventions such as phototherapy (353), vagus nerve stimulation (356), or repetitive transcranial magnetic stimulation (357) requires further study.

C. Rapid Cycling

Rapid cycling is generally difficult to treat (358,359). An important first step is to assess for and treat medical conditions that may contribute to cycling, such as hypothyroidism or drug or alcohol use. Medications, particularly antidepressants, may also contribute to cycling. Such medications should be discontinued if possible. Increases in cycling frequency or precipitation of hypomanic or manic episodes have been reported in association with essentially all currently approved antidepressants (340,343,360). Use of some form of mood chart can aid in identifying a link between a medication and cycling frequency.

Rapid cycling is relatively unresponsive to lithium or carbamazepine (358,361-363). Among 41 lithium-treated patients with rapid-cycling bipolar disorder followed for 5 years, all patients experienced at least one recurrence. Twenty-six percent derived limited or no prophylactic benefit (364). The limited benefit of lithium in rapid cycling may be a function of its lack of efficacy for depressive symptoms, despite its efficacy for manic symptoms (365,366). In the open-stabilization phase of a study of lithium and divalproex in patients with rapid-cycling bipolar disorder, those who failed to meet criteria for random assignment were more likely to have refractory depression (76%) than manic or mixed states (24%) (40). These results suggest that 1) the major benefit of treatment with lithium or lithium combined with divalproex is on the manic aspects of rapid-cycling bipolar disorder and 2) rapid cycling is principally characterized by recurrent depression.

In a randomized, blind, placebo-controlled study of 182 patients with rapid-cycling bipolar I or bipolar II disorder who were receiving maintenance treatment (39), lamotrigine was superior to placebo on overall study survival ($p < 0.04$) but not on the primary measure, which was the time elapsed until the onset of a mood episode that required additional pharmacotherapy. The lamotrigine over placebo advantage was greatest ($p = 0.01$) among the 52 patients with bipolar II disorder: the median time to discontinuation for any reason among patients with bipolar II disorder was 17 weeks for the patients receiving lamotrigine and 7 weeks for those given placebo (the discontinuation times among the entire group were 18 weeks and 12 weeks for the lamotrigine-treated and placebo-treated patients, respectively). Similarly, the rate of study completion without relapse in patients receiving medication monotherapy was significantly greater among the lamotrigine-treated than among the placebo-treated patients with bipolar II disorder (46% versus 18%, $p = 0.04$); this difference was not seen among those with bipolar I disorder (39). An open study comparing response to lamotrigine in patients with rapid-cycling versus non-rapid-cycling bipolar disorder also indicated efficacy, with some evidence that rapid-cycling patients with more severe manic symptoms at the start of treatment respond less well (367).

Divalproex was effective as monotherapy or as an add-on therapy in an open study of 107 rapid-cycling patients followed for a mean of 17 months. Marked benefit occurred among 77% of the patients who entered the study when manic or hypomanic. However, only 38% of those who entered the study depressed reached the maintenance stage (368,369).

These limited data provide support for the use of lamotrigine in rapid-cycling bipolar disorder—especially for depressive features, which appear to dominate the bipolar II form of rapid cycling—and suggest that combination drug therapy is often superior to use of a single drug.

D. Maintenance Treatment

Maintenance treatment of patients with bipolar disorder has multiple goals. In addition to relapse prevention, reduction of subthreshold symptoms, and reduction of suicide risk, aims need to include reduction of cycling frequency and mood instability as well as improvement of functioning. Maintenance medication is generally recommended following a manic episode (370,371). Although few studies involving patients with bipolar II disorder have been conducted in this area, consideration of maintenance treatment for this form of the illness is also strongly warranted.

Maintenance studies pose two difficulties not central to acute episode studies. The multiple treatment goals make it impractical to

select a single goal as an adequate index of efficacy. Also, because of risks associated with full relapse and of suicidal behavior, few placebo-controlled studies have been conducted, and many of those have enrolled somewhat less severely ill patients than seen in the spectrum of clinical practice with bipolar disorder (372).

This section will present efficacy data on lithium, anti-convulsants, antipsychotics, and ECT as maintenance treatment agents. Information on side effects and implementation and dosing issues for lithium and the anticonvulsants are presented in this guideline in their respective sections under "Somatic Treatments of Acute Manic and Mixed Episodes" (section V.A.), with the exception of lamotrigine, the data for which are presented under "Somatic Treatment of Acute Depressive Episodes" (section V.B.2.c.).

1. Lithium

Studies conducted over 25 years ago consistently reported lithium to be more effective than placebo with regard to the proportion of patients who did not relapse (373-377). Most of these studies used discontinuation study designs, in which patients taking stable doses of lithium were abruptly discontinued from lithium if randomly assigned to placebo. It has subsequently become clear that such discontinuation of lithium increases early relapse into mania or depression (378). These studies had additional design limitations, including enrollment of both unipolar and bipolar depressed patients, lack of specification of diagnostic criteria, reporting of results only for patients who completed the study, and failure to report reasons for premature discontinuation. These studies raised expectations for lithium therapy unrealistically.

In large, open, naturalistic studies on the effectiveness of lithium as a maintenance treatment agent in patients with bipolar disorder, good outcomes (e.g., no relapse and only mild symptoms) were seen in approximately one-third of the subjects (226,364,379-382). At a 2-year follow-up evaluation, Markar and Mander (379) reported no difference in the rate of hospital readmissions between patients who received lithium and those who did not. Harrow et al. (380) reported equivalent 1-year outcomes for patients receiving lithium and those not taking medication, with 40% of patients taking lithium for the year developing manic episodes. Coryell et al. (381) reported a lower risk of relapse during the first 32 weeks of treatment for patients taking lithium than for those receiving no prophylactic medication, but no difference in relapse risk was seen for weeks 33-96. Other large, open studies that have employed varying methods have reported similar results (226,364,383,382). In general, these studies have also reported high dropout rates.

However, two recent randomized, double-blind, parallel-group studies have indicated evidence of efficacy for lithium compared with placebo in extending time until a new manic episode (385,386). Each study enrolled patients who were currently experiencing or recently had experienced a manic episode. Symptoms were initially controlled through open treatment with medications (including those to which the subjects would be randomly assigned). Subjects were then randomly assigned either to treatment with lithium, placebo, or divalproex (385) or treatment with lithium, placebo, or lamotrigine (386). The first study measured the time until 25% of subjects under-going 1 year of maintenance lithium treatment suffered recurrent mania. In this study, lithium extended the time until recurrence by 55% compared with placebo (385). In the second study, an 18-month trial that enrolled patients during or shortly after a manic episode, lithium significantly extended time until intervention for a recurrent manic episode relative to placebo ($p=0.006$). The relapse rate into mania was 17% for lithium-treated patients, compared with 41% for placebo-treated patients (386). However, lithium did not significantly extend time until a new depressive episode in either study and tended to worsen sub-threshold depressive symptoms in the first study (385). These two studies were the first maintenance studies to use modern methods, enroll patients during an index manic episode, and taper lithium taken during the open phase for those patients entering the randomized, placebo-controlled maintenance phase. Earlier randomized, placebo-controlled studies and a crossover study also have reported efficacy for lithium with regard to manic, but not depressive, symptoms (362,365,366).

A randomized, open 2.5-year study compared lithium maintenance treatment with that of carbamazepine (387). The primary efficacy measure, time until hospitalization, did not indicate a significant difference between the treatments. However, broader secondary analyses, such as time until relapse or need for concomitant medication, favored lithium (44% versus 67%, $p=0.04$). Rapid cycling is associated with relatively poor response to lithium (358); however, in a small prospective study, both rapid-cycling and non-rapid-cycling patients had fewer manic episodes with lithium therapy than did those receiving placebo (365). In addition, one small study has suggested that combining lithium and carbamazepine improves the proportion of response among rapid-cycling patients to a rate equivalent to that of non-rapid-cycling patients (362).

Serum-level guidelines are not well established for maintenance treatment with lithium. In clinical settings, doses and serum levels somewhat lower than those employed for treatment of acute mania are generally used (316). One randomized study of high- and low-dose lithium ranges indicated better efficacy for lithium at 0.8-1.0 meq/liter than at 0.4-0.6 meq/liter in the prevention of manic, but not depressed, episodes (225). However, tolerability was much worse at the higher range. An open study similarly reported rates of rehospitalization lower than those before treatment for the subset of patients whose serum levels were consistently above 0.5 meq/liter (364).

2. Divalproex or valproate

Valproate has been studied in one placebo-controlled, double-blind, randomized trial (385) and two randomized comparisons with lithium (254,388). In the placebo-controlled study, there was no significant difference in the primary efficacy measure (time until development of any mood episode) among patients treated with divalproex, lithium, and placebo, although there was a nonsignificant difference favoring divalproex over lithium ($p=0.06$). Divalproex was superior to placebo on rate of early termination for any mood episode (24% versus 38%, respectively; $p<0.02$), early termination for depression (6% versus 16%; $p<0.02$), and termination due to failure to adhere to protocol, intercurrent illness, or administrative reasons (16% versus 25%; $p<0.02$). Early termination for intolerance or noncompliance favored divalproex over lithium (22% versus 35%, respectively; $p<0.03$). The divalproex advantage over placebo was greater in the subset of 149 patients who had received divalproex treatment for their manic episode during the open period, with rates of early termination for any mood episode of 29% and 50%, respectively ($p<0.04$). One randomized, 18-month open study of valproate (formulated as valpromide) versus lithium reported a 20% lower rate of new episodes among valpromide-treated patients than among lithium-treated patients (388). Relative to patients given lithium, a lower proportion of patients given valpromide had their treatment discontinued because of intolerance or lack of efficacy. Divalproex and lithium were comparably effective in a 1-year, open, naturalistic, longitudinal study that allowed addition of any needed medication (254). Finally, divalproex was effective both as monotherapy and when added to lithium therapy in a large, open maintenance trial of patients with rapid-cycling presentations (368). These findings indicate efficacy and generally good tolerability of divalproex in maintenance treatment, with effectiveness at least comparable to lithium.

As with lithium, dosing guidelines for maintenance treatment are less evidence-based than for acute treatment of mania, and lower levels are sometimes used for maintenance treatment. A 1-year study of divalproex found an association between higher serum levels and increased appetite, reduced platelet counts, and reduced WBC counts (371).

3. Lamotrigine

Lamotrigine has been studied in one large, 18-month, randomized, double-blind, placebo-controlled study of patients who had experienced a manic or hypomanic episode within 60 days of entry into an open treatment phase (386). Patients who improved during the open-treatment phase were randomly assigned to maintenance treatment with lamotrigine, lithium, or placebo. For the primary outcome measure (time until additional pharmacotherapy required for treatment of a mood episode), both lamotrigine and lithium were superior to placebo ($p < 0.02$ and $p = 0.003$, respectively). The median time until one-quarter of the patients in each treatment group developed a mood episode was 72 weeks for those given lamotrigine, 58 weeks for those receiving lithium, and 35 weeks for those given placebo. On a secondary outcome measure (time until discontinuation for any reason), lamotrigine was superior to placebo, but lithium was not ($p = 0.03$ and $p = 0.07$, respectively). Lamotrigine did not significantly prolong the time until a manic episode but was superior to placebo in prolonging the time until a depressive episode ($p < 0.02$), whereas lithium was not ($p < 0.17$). Lamotrigine was also superior to placebo in a 26-week study of rapid-cycling patients with bipolar I or bipolar II disorder (39). The primary efficacy measure, time until additional medication required for treatment of a mood episode, did not differ significantly ($p = 0.07$). However, among patients with bipolar II disorder, the median time until additional pharmacotherapy was required was significantly greater for those receiving lamotrigine than for those given placebo (17 weeks versus 7 weeks, $p = 0.01$). Time until additional pharmacotherapy was required did not differ significantly among patients with bipolar I disorder. Also, the proportion of patients who completed the study without requiring additional medication was greater among those treated with lamotrigine than for those given placebo (41% versus 26%, $p = 0.03$). Among patients requiring additional pharmacotherapy, 80% required medication for depressive symptoms; 20% required medication for manic, hypomanic, or mixed symptoms (39). These results are consistent with those of an open study of patients with bipolar disorder treated with lamotrigine for up to 48 weeks either as monotherapy or as part of combination therapy (329).

4. Carbamazepine

The effectiveness of carbamazepine for maintenance treatment of bipolar disorder is unclear (362). Carbamazepine was inferior to lithium on most outcome measures in one randomized, open, 2.5-year study (387). Carbamazepine was nonsignificantly better than lithium among patients with mood-incongruent illnesses, comorbidity, mixed states, and bipolar II disorder (389). Crossover studies have reported carbamazepine somewhat less effective than lithium in maintenance treatment of bipolar disorder (362,390). The proportion of time spent in a manic episode dropped from 25% before treatment to 19% in patients treated with carbamazepine and 9% in patients treated with lithium ($p < 0.01$). The proportion of time spent in a depressive episode did not change after initiation of either drug (before treatment: 32%, in patients treated with carbamazepine: 26%, in patients treated with lithium: 31%) (362).

5. Antipsychotic medications

The one placebo-controlled study of prophylactic treatment with an antipsychotic drug did not show an advantage of flupentixol plus lithium compared with lithium alone (391). Open case reports and one randomized, open study of clozapine plus usual care compared with usual care alone have indicated benefits of maintenance clozapine treatment over 1 year (303).

6. ECT

The use of ECT on a maintenance basis to prevent mood episodes in patients with bipolar disorder was initially described over 50 years ago (392,393). While efficacy of maintenance ECT for bipolar disorder patients has never been assessed in a randomized, controlled trial, multiple case reports and case series have suggested its utility (51,356,394-403). A more extensive naturalistic review (404) identified 56 patients, including nine with bipolar disorder, who received maintenance ECT following successful index treatment. Of the patients with bipolar disorder, 78% showed at least some improvement, and 33% were much improved.

Vanelle et al. (405) prospectively followed 22 medication-resistant or medication-intolerant patients for more than 18 months of maintenance ECT treatment. Seven of these individuals were diagnosed with bipolar disorder, and four had shown a rapid-cycling course. When the study period was compared with the 1-year period before ECT initiation, the maintenance ECT group as a whole showed a significant decrease in time spent in the hospital and in the number of episodes of illness that necessitated hospitalization. For the patients with bipolar disorder, as well as in those with major depressive disorder, the mean number of mood episodes significantly decreased during the maintenance ECT course. None of the bipolar disorder patients failed to show a response to maintenance ECT.

Schwarz et al. (406), using a case-control approach, compared depressed patients who responded to an acute course of ECT and then received maintenance ECT to patients who responded to acute ECT but received no maintenance ECT. A third comparison group received only pharmacotherapy. In each group, four of the 21 patients had a diagnosis of bipolar disorder. Although this number was too small to permit subgroup analysis, the rate of rehospitalization decreased by 67% for the study patients as a whole with implementation of maintenance ECT. In depressed patients who had responded to an acute course of ECT, Gagné et al. (407) also used a case-control approach to compare patients who received maintenance pharmacotherapy alone with those who received maintenance ECT in combination with maintenance pharmacotherapy. The two groups differed only in the number of "adequate" pharmacotherapy trials before ECT, with patients receiving maintenance ECT showing greater resistance to pharmacotherapy. Of the 58 depressed patients in the study, 12 had a diagnosis of bipolar disorder. For the group as a whole, patients receiving maintenance ECT had a greater cumulative probability of surviving without relapse or recurrence at 2 years than patients receiving only pharmacotherapy after the index ECT course (93% versus 52%, respectively). At 5 years, the difference in survival between the two groups was even more striking (73% versus 18%, respectively). Proportional hazards regression did not demonstrate statistically significant rate differences between patients with bipolar disorder and those with major depressive disorder.

Thus, in studies of maintenance ECT, study group sizes have been small, and patients with bipolar disorder have made up a small proportion of those groups, making subgroup analyses impossible. Nonetheless, the findings suggest that maintenance ECT may be helpful for individual patients with severe bipolar illness who are unable to tolerate or do not respond to maintenance pharmacotherapy.

E. Psychosocial Interventions

Although psychiatric management and pharmacotherapy are essential components of bipolar disorder treatment, specific forms of psychotherapy also are critical components of the treatment plan for many patients. Patients with bipolar disorder suffer from the psychosocial consequences of past episodes, the ongoing vulnerability to future episodes, and the burdens of adhering to a long-term treatment plan that may involve unpleasant side effects. In addition, many patients have clinically significant residual symptoms or mood instability between major episodes. The primary goals of psychotherapeutic treatments are to reduce distress and improve the patient's functioning between episodes as well as decrease the likelihood and severity of future episodes (408).

Most patients with bipolar disorder struggle with some of the following issues: 1) emotional consequences of episodes of mania and depression; 2) coming to terms with having a potentially chronic mental illness; 3) problems associated with stigmatization; 4) delays or major deviations in development; 5) fears of recurrence and consequent inhibition of more autonomous functioning; 6) interpersonal difficulties, including issues pertaining to marriage, family, childbearing, and parenting; 7) academic and occupational problems; and 8) other legal, social, and emotional problems that arise from reckless, inappropriate, withdrawn, or violent behavior that may occur during episodes. Although a specific psychotherapeutic approach (in addition to psychiatric management) may be needed to address these issues, the form, intensity, and focus of psychotherapy will vary over time for each patient.

There are now a range of specific psychotherapeutic interventions that have been shown to be helpful when used in combination with pharmacotherapy and psychiatric management for treatment of bipolar disorder. The best-studied treatment approaches have been developed around psychoeducational, interpersonal, family, and cognitive behavior therapies. Formal studies have been conducted for these treatments, and additional investigations are underway. Further, psychodynamic and other forms of therapy may be indicated for some patients. The available psychotherapeutic treatments are discussed as separate entities, even though psychiatrists commonly use a combination or synthesis of different approaches depending on both training and the patient's needs and preferences.

1. Efficacy

Evidence concerning the utility of specific psychosocial interventions for patients with bipolar disorder is slowly building. The research summarized here involves the specific forms of psychotherapy that have been studied in randomized, controlled clinical trials.

Perry et al. (27) evaluated a relatively brief (average: seven sessions) individual psychoeducational intervention that focused on illness management, recognition of risk factors, and prevention of relapses. When compared with a group randomly assigned to a treatment-as-usual condition, patients receiving psychoeducation (in addition to pharmacotherapy) experienced a significant reduction in risk of manic relapses as well as improved social and vocational functioning.

A brief (approximately six sessions) inpatient family intervention (409) has been developed for patients with schizophrenia or bipolar disorder. Goals include accepting the reality of the illness, identifying precipitating stressors and likely future stressors inside and outside the family, elucidating family interactions that produce stress on the patient, planning strategies for managing or minimizing future stressors, and bringing about the patient's family's acceptance of the need for continued treatment after hospital discharge. In the initial study (410), the family intervention resulted in improved outcomes for female patients with affective disorders but not for male patients. In a subsequent study by this group (410), ongoing couples therapy (extending for up to 11 months after hospitalization) was found to significantly enhance treatment adherence and improve global functioning. Unfortunately, this study was too small (intent-to-treat N=42) to reliably detect more modest effects, such as a reduction of relapse risk.

When the functional impairments of bipolar disorder are severe and persistent, other services may be necessary, such as case management, assertive community treatment, psychosocial rehabilitation, and supported employment. These approaches, which have traditionally been studied in patients with schizophrenia, also show effectiveness for certain individuals with bipolar disorder.

Family-focused treatment was developed for patients who have recently had an episode of mania or depression (411). Family-focused therapy is behaviorally based and includes psychoeducation, communication skills training, and problem-solving skills training. One adequately sized trial of behavioral family treatment has been completed; the investigators found that behavioral family management (in concert with adequate pharmacotherapy) resulted in a substantial decrease in depressive relapse rates when compared with a treatment-as-usual control condition (412).

A cognitive behavior therapy program for patients with bipolar disorder has been developed by Basco and Rush (413). The goals of the program are to educate the patient regarding bipolar disorder and its treatment, teach cognitive behavior skills for coping with psychosocial stressors and attendant problems, facilitate compliance with treatment, and monitor the occurrence and severity of symptoms. A large study of the impact of cognitive behavior therapy for prophylaxis against bipolar recurrences is underway. Preliminary studies suggest that this approach may help reduce depressive symptoms (414), improve longer-term outcomes (415), and improve treatment adherence (416).

The observation that many patients with bipolar disorder experience less mood lability when they maintain a regular pattern of daily activities (including sleeping, eating, physical activity, and emotional stimulation) has led to the development of a formalized psychotherapy called interpersonal and social rhythm therapy (417). This form of psychotherapy builds upon the traditional focus of interpersonal psychotherapy by incorporating a behavioral self-monitoring program intended to help patients with bipolar disorder initiate and maintain a lifestyle characterized by more regular sleep-wake cycles, meal times, and other so-called social zeitgebers. The ultimate goal is to help regulate circadian disturbances that may provoke or exaggerate episodes of mood disorder.

Frank and colleagues have reported several findings from their ongoing study of interpersonal and social rhythm therapy. First, interpersonal and social rhythm therapy (in combination with pharmacotherapy) was associated with significant increases in targeted lifestyle regularities when compared with a clinical management plus pharmacotherapy control group (418). However, interpersonal and social rhythm therapy was not associated with a faster time to recovery from manic (419) or depressive (420) episodes. The withdrawal of interpersonal and social rhythm therapy after stabilization was associated with a significant increase in relapse rates (421). Across 2 years of maintenance treatment, interpersonal and social rhythm therapy led to a reduction of both depressive symptoms and manic/hypomanic symptoms and an increase in days of euthymia when compared with treatment as

usual (unpublished 2001 study of E. Frank and D.J. Kupfer).

Finally, preliminary results of a trial comparing group psychoeducation to standard medical care alone among a group of patients with bipolar disorder suggest that patients receiving psychoeducation had significantly fewer manic episodes, depressive episodes, and hospitalizations (422).

2. Psychotherapeutic treatment of mania

Psychosocial therapies alone are generally not useful treatments for acute mania. Perhaps the only indications for psychotherapy alone are when all established treatments have been refused, involuntary treatment is not appropriate, and the primary focus of therapy is focused and crisis-oriented (e.g., resolving ambivalence about taking medication). In one study of bipolar I disorder patients with acute mania or hypomania, treatment with the combination of interpersonal and social rhythm therapy and pharmacotherapy did not produce an additive effect on manic symptoms or reduce time to remission when compared with an intensive clinical paradigm plus medication (419). Moreover, patients withdrawn from this psychotherapy after completion of acute treatment had a poorer prognosis when compared with those who either received monthly maintenance psychotherapy sessions or recovered with intensive clinical management and pharmacotherapy (421).

3. Psychotherapeutic treatment of depression

Several psychotherapeutic approaches, including cognitive behavior therapy (423) and interpersonal therapy (424-426), have demonstrated efficacy in patients with unipolar depression, either in lieu of or in addition to pharmacotherapy. Efficacy data are discussed in the APA *Practice Guideline for the Treatment of Patients With Major Depressive Disorder* (2).

For unipolar depression, the application of a specific, effective psychotherapy in lieu of pharmacotherapy may be considered for patients with mild to moderate symptoms. For bipolar depression, the use of focused psychotherapy instead of antidepressant pharmacotherapy has potential appeal, particularly with respect to avoiding antidepressant side effects and minimizing the risk of treatment-emergent mania or induction of rapid cycling. However, only a handful of reports have described such an approach, and there have been no definitive studies to date.

Cole et al. (420) evaluated the impact of a modified form of interpersonal psychotherapy as part of a larger study relating thyroid function to clinical course in 65 patients with bipolar I depression. Patients were randomly assigned to receive weekly interpersonal and social rhythm therapy sessions or treatment as usual. All patients received pharmacotherapy (principally lithium salts); about two-thirds of the patients also received antidepressants. Cole et al. found that the addition of weekly psychotherapy did not enhance depressive symptom reduction or accelerate time to remission in comparison with treatment as usual across up to 6 months of treatment.

Zaretsky et al. (414) treated 11 patients with bipolar depression with individual cognitive behavior therapy (20 weekly sessions) in addition to ongoing pharmacotherapy. They compared their patients' outcomes to a contemporaneous group of age and sex-matched patients with unipolar depression. Among the eight completers in the bipolar depression group (seven with bipolar I disorder, one with bipolar II disorder), improvements were comparable to those in the unipolar depression group. Further, no depressed patient receiving cognitive behavior therapy developed treatment-emergent mania or hypomania.

4. Maintenance treatment

Since the 1994 publication of the first APA practice guideline for bipolar disorder (5), a number of reports on the value of concomitant psychosocial treatment during the maintenance phase of treatment for bipolar disorder have been published. All studies used "add-on" designs, with patients continuing pharmacotherapies such as lithium and divalproex. Many of these reports described preliminary or pilot studies; nevertheless, results of three larger, more definitive studies have been published for psychoeducation (27), interpersonal and social rhythm therapy (427), and family-focused (412) interventions.

Overall, these studies demonstrated that the addition of a time-limited individual psychosocial intervention appropriately modified for bipolar disorder is likely to improve outcomes across 1-2 years of follow-up. When feasible, group psychoeducational interventions also appear useful (428), which may improve the cost efficiency of treatment. Despite these promising results, however, improvements have not been consistently documented across studies on the full range of syndromal, functional, adherence, and interpersonal domains. On the basis of a methodological review of the more numerous studies of unipolar depression (429), such inconsistencies in findings are more likely to be attributable to differences in patient populations and statistical power than true therapeutic specificity.

Nevertheless, the weight of the evidence suggests that patients with bipolar disorder are likely to gain some additional benefit during the maintenance phase from a concomitant psychosocial intervention, including psychotherapy, that addresses illness management (i.e., adherence, lifestyle changes, and early detection of prodromal symptoms) and interpersonal difficulties. The more commonly practiced supportive and dynamic-eclectic therapies have not been studied in randomized, controlled trials as maintenance treatments for patients with bipolar disorder.

5. Addressing comorbid disorders and psychosocial consequences

Patients in remission from bipolar disorder suffer from the psychosocial consequences of past episodes and ongoing vulnerability to future episodes. In addition, patients with this disorder remain vulnerable to other psychiatric disorders, including, most commonly, substance use disorders (66) and personality disorders (430,431). Each of these comorbid disorders has particular consequences and increases the overall psychosocial vulnerability of the patient with bipolar disorder. Psychosocial treatments, including psychotherapy, should address issues of comorbidity and complications that are present.

F. Somatic Therapies for Children and Adolescents

To date, there has been only one double-blind, placebo-controlled, randomized study of pharmacotherapy in the treatment of adolescents with bipolar disorder (432). The majority of information available about pharmacological treatments for bipolar disorder in youth relies upon open studies, case series, and case reports.

1. Lithium

There are more data available for lithium than for any other medication in the treatment of bipolar disorder in children and adolescents. Geller et al. (432) conducted the only double-blind, placebo-controlled, parallel-group study of lithium treatment in 25 adolescent outpatients with comorbid bipolar disorder and substance dependence. Subjects were randomly assigned to lithium or placebo for a 6-week trial. There was significantly greater improvement in global functioning with lithium treatment than with placebo. Significantly more patients in the lithium-treatment group experienced thirst, polyuria, nausea, vomiting, and dizziness.

In four double-blind, placebo-controlled, crossover studies of children with bipolar disorder, significant improvement in mood lability, explosive outbursts, aggressive behavior, and psychosis was found with lithium compared with placebo (433-436). However, small study group sizes, diagnostic issues, and short treatment durations limit the interpretation of these findings. There have also been open studies, case series, and case reports with clinical responses ranging from 50% to 100% (437-455).

2. Valproate/divalproex

There have been no placebo-controlled studies of divalproex in the treatment of bipolar disorder in children and adolescents, but divalproex response rates in four open studies ranged from 60% to 83% (127,456-458).

In the only multisite open study of divalproex treatment for children and adolescents with bipolar disorder (458), 40 subjects ages 7-17 years received divalproex for 2-8 weeks. Sixty-one percent of the subjects showed a 50% improvement from baseline scores on the Young Mania Rating Scale. Twenty-three patients (58%) discontinued the study, of whom 16 had a comorbid psychiatric diagnosis such as ADHD, conduct disorder, or oppositional defiant disorder. The most commonly occurring side effects (>10% incidence) were headache, nausea, vomiting, diarrhea, and somnolence. No significant laboratory abnormalities were noted.

There have also been four case reports or series of divalproex sodium treatment of bipolar disorder in youth. Response rates have ranged from 66% to 100% in these reports (459-462).

Divalproex also showed efficacy in an active-comparator study in which 42 children and adolescents (ages 8-18 years) with bipolar disorder were randomly assigned to 6 weeks of open treatment with lithium, divalproex, or carbamazepine (463). No significant differences in response rates (>50% change from baseline to last Young Mania Rating Scale score) were found among the patients receiving divalproex (53%), lithium (38%), or carbamazepine (38%). There were no serious adverse events reported with any of these medications.

In the continuation phase of this study, 35 patients received open treatment for an additional 16-18 weeks (463). Response during the continuation phase was defined as a score of 1 or 2 on the Bipolar Clinical Global Improvement Scale. Thirty patients (85%) were classified as having responded at the end of the continuation phase. Only 13 patients (37%) were receiving a single study drug (lithium, divalproex, or carbamazepine) and no other psychotropic medication at the end of the continuation phase. For the 22 patients who required additional psychotropic medication, 11 received a second study drug (lithium, divalproex, or carbamazepine), and 11 received a stimulant.

3. Carbamazepine

Information about the use of carbamazepine in the treatment of adolescent bipolar disorder is limited to case reports. Woolston (464) described three cases of carbamazepine monotherapy for adolescents with bipolar disorder in whom clinical improvement of manic symptoms was demonstrated. A positive response was reported with the combination of carbamazepine and lithium in seven adolescents with bipolar disorder (192,449).

4. Atypical antipsychotics

There are two case series and one open trial of olanzapine as primary or adjunctive treatment for children and adolescents with bipolar disorder. In an open study, 23 children ages 5-14 years with bipolar disorder received olanzapine 2.5-20 mg/day for 8 weeks (465). Response was defined as \geq 30% improvement in score on the Young Mania Rating Scale, and the response rate was 61%. There were no significant side effects reported except weight gain (mean=5 kg). In case reports of three youths (ages 9-19 years) with bipolar disorder, olanzapine was used as an adjunctive treatment in addition to existing medication regimens (466). Within a week, CGI scores were rated markedly improved. Sedation and weight gain were the common side effects. Finally, in a report of seven cases of adolescents with bipolar disorder (467), olanzapine was used as adjunctive treatment to existing psychotropic medication regimens. Seventy-one percent of adolescents showed marked to moderate response on CGI scores with adjunctive olanzapine treatment.

A retrospective chart review of 28 outpatient children and adolescents ages 4-17 years with bipolar disorder assessed adjunctive risperidone treatment (468). These subjects received risperidone over an average of 6 months. Improvement (CGI score \leq 2) in manic and aggressive symptoms was seen in 82% of the patients, and 69% exhibited improvement in psychotic symptoms. No serious adverse effects were reported, although common side effects were weight gain and sedation.

5. Newer antiepileptics

There are few reports of the use of the newer antiepileptic agents in the treatment of children and adolescents with bipolar disorder. In a retrospective study of 18 adolescents for whom prior medication trials had failed (469), subjects with bipolar disorder not otherwise specified (N= 15), bipolar II disorder (N=1), or schizoaffective disorder (N=2) received gabapentin at doses between 900 and 2400 mg/day. Sixteen of the adolescents who continued gabapentin treatment had cessation of cycling. Of these patients, six reported improved mood. Gabapentin was also reported to be effective in the treatment of an adolescent patient with mania (470).

6. ECT

ECT has been used to treat refractory mania in two prepubertal children (471). A review of literature on ECT use in young people (472) reported its efficacy for mania in adolescents.