BIPOLAR DISORDER

an overview of current treatment with a focus on the role of calcium channel blockers

THIS ACTIVITY IS SPONSORED BY
POSTGRADUATE INSTITUTE
FOR MEDICINE

RELEASE DATE: APRIL 2000
LAST REVIEW DATE: MARCH 2000
EXPIRATION DATE: APRIL 2002
ESTIMATED TIME TO COMPLETE
THIS ACTIVITY: 2 HOURS

Supported through an unrestricted educational grant from Bayer Corporation, Pharmaceutical Division.

STATEMENT OF NEED

As bipolar disorder has been better recognized in the past decade, so have patients who do not respond to standard pharmacotherapies. These patients often challenge psychiatrists, who must consider medications in an off-label use to effectively treat these patients. Of the several drug classes which have proven useful in treating these patients, calcium channel blockers are an ongoing area of interest. Clinicians learning more about the calcium channel blockers and their role in the treatment of bipolar disorder will be more capable in their approach to the patient with resistant illness.

LEARNING OBJECTIVES AND TARGET AUDIENCE

This monograph *Bipolar Disorder: an overview of current treatment with a focus on the role of calcium channel blockers* is designed for physicians.

After completing this continuing education program, the participants should be able to:

- Describe the standard treatment modalities that are commonly used in the treatment of bipolar disorder
- Describe examples of treatment with various medications in off-label use that can be therapeutic in individuals with resistant illness
- Explain the role of calcium channel blockers in the treatment of resistant cases of bipolar disorder
- Give examples of treatment regiments using calcium channel blockers that may be useful in resistant cases of bipolar disorder.

FACULTY

Postgraduate Institute for Medicine has a conflict of interest policy that requires course faculty to disclose any real or apparent commercial financial affiliations related to the content of their presentations/materials. It is not assumed that these financial interests or affiliations will have an adverse impact of faculty presentations; they are simply noted here to fully inform participants.

Moderator: Steven A. Weisblatt, MD
Associate Professor of Clinical Psychiatry
Albert Einstein College of Medicine, Bronx, NY
Grants/Research Support from Bayer Pharmaceuticals, and Speaker's Bureau for Abott Laboratories.

Steven L. Dubovsky, MD
Professor of Psychiatry and Medicine
Interim Chairman, Department of Psychiatry
University of Colorado Health Sciences Center, Denver, CO
Grants/Research Support from Eli Lilly and Co., Pfizer, and Parke-Davis.

P. J. Pazzaglia, MD
Associate Professor
Department of Psychiatry
University of Texas Medical School - Houston, Houston, TX
No relationship with any commercial entity disclosed.

Paul J. Goodnick, MD, FABPN, FAPA,
Professor of Psychiatry and Behavioral Sciences
Director, Mood Disorder Program
Certified Psychopharmacology ASCP
University of Miami School of Medicine, Miami, FL
No relationship with any commercial entity disclosed.

Robert M. Post, MD
Chief, Biological Psychiatry Branch
National Institute of Mental Health
National Institutes of Health, Bethesda, MD
Consultant for Eli Lilly and Co., Parke-Davis, Glaxo Wellcome, Bayer Corporation, and Janssen Pharmaceutical.

Postgraduate Institute for Medicine does not view the existence of these relationships to imply bias or that the value of the material is decreased. The content of this CME activity was planned to be balanced, objective, and scientifically rigorous. Occasionally, authors may express opinions that represent their own viewpoint. Conclusions drawn by participants should be derived from objective analysis of scientific data.

This monograph is based on a roundtable panel discussion.

TABLE OF CONTENTS

ACCREDITATION AND DESIGNATION

This activity has been planned and implemented in accordance with the Essentials and Standards of the Accreditation Council for Continuing Medical Education (ACCME) through the joint sponsorship of Postgraduate Institute for Medicine (PIM) and Health Management Solutions, Inc. The Postgraduate Institute for Medicine is accredited by the ACCME to provide continuing medical education for physicians and takes responsibility for the content, quality and scientific integrity of this CME activity.

Postgraduate Institute for Medicine designates this educational activity for a maximum of 2 hours in category 1 credit towards the AMA Physician's Recognition Award. Each physician should claim only those hours of credit that he/she actually spent in the educational activity.

Any procedures, medications, or other courses of diagnosis or treatment discussed or suggested in this activity should not be used by clinicians without evaluation of their patient's conditions and possible contraindications on dangers in use, review of any applicable manufacturer's product information, and comparison with recommendations of other authorities.

I. EPIDEMIOLOGY

Bipolar disorder is a major public health problem. Estimates of lifetime prevalence vary. The Epidemiological Catchment Area (ECA) Study indicates that bipolar I and II disorders combined are more prevalent than previously estimated.[1] Over the course of a lifetime, bipolar I disorder affects approximately 0.8% of the adult population and bipolar II disorder, about 0.5%.[2]

Classic bipolar disorder may have a prevalence of 1.0% to 1.6% in the United States and 0.3% to 1.5% worldwide.[3-5] One cohort study held in Zurich reported a 5.5% prevalence for the disorder.[6] With the inclusion of diagnoses, such as cyclothymia, that fall within the spectrum of bipolar disorders, estimates increase to 3% to 6.5%.

Bipolar disorder is associated with a significant risk of mortality. Approximately 25% of patients attempt suicide, and some 10% to 15% succeed.[7,8] Patients with the disorder are also at increased risk for violence and homicide. Occupational status decreases in up to two thirds of patients, and functioning decreases up to 50% of normal.

Many patients with unipolar depression may have unrecognized or undiagnosed bipolar disorder. Of 559 patients in the National Institute of Mental Health Collaborative Depression Study, 3.9% were eventually diagnosed with bipolar I disorder and 8.6% with bipolar II disorder on follow-up over 2 to 11 years.[9]

Dysphoric mania, or mixed mania, a severe and recalcitrant form of bipolar illness, occurs in about 30% to 40% of all manic episodes.[10] It is more often associated with female gender, suicide, early onset, long duration, high rates of personal and family depression, substance abuse, and neuropsychiatric abnormalities.[11] Recent data indicate that since World War II, both unipolar and bipolar depression have an increased incidence in successive generations, possibly due to genetic or environmental factors.[12-14]

In 1990, the economic burden of bipolar disorder in the United States was estimated to be $15.5 billion in diminished or lost productivity in work performance alone.[15] Treated patients lost an estimated 152 million cumulative days from work; untreated patients lost 137 million. Undertreatment of bipolar disorder is a significant factor in weighing its potential costs, as it is estimated that one third of untreated patients could be treated successfully.

Theoretically, efficient treatment of bipolar disorder would save $10.5 billion in the first year.[16] Because bipolar illness is a lifetime disorder, economic analyses need to review a longer period of time when calculating costs and benefits.

> *"In 1990, the economic burden of bipolar disorder in the United States was estimated to be $15.5 billion in diminished or lost productivity in work performance alone.[15]"*

AGE

The ECA study reported a mean age of onset of 21 years for both types of bipolar disorder.[2] Some investigators have observed a bimodal distribution, with a primary peak in early adulthood and a secondary peak in the 40s to late 50s. Others have noted a unimodal distribution. A significant time lag may occur between the onset of illness and the first treatment. In a survey of members of the National Depressive and Manic Depressive Association, more than half did not seek care for 5 years after first experiencing symptoms, and 36% did not seek care for more than 10 years,[17] depending on diagnosis.

Bipolar disorder is undiagnosed or misdiagnosed for an average of 8 years after the initial episode. Over 60% of patients are untreated, undertreated, or inappropriately treated at some time, placing them at increased risk for morbidity with detrimental effects on personality, school, and work and social functioning and possibly diminishing their response to subsequent treatment.

Bipolar illness of early onset is more commonly associated with rapid cycling, mixed states, substance abuse, and psychotic features. It may be also more likely to respond to treatment with drugs other than lithium.

II. SPECTRUM OF ILLNESS

GENDER

Overall, the incidence of bipolar spectrum disorder is slightly greater in females than it is in males, with a gender ratio of 1.2:1. Among rapid cyclers, this ratio is particularly high,[18] with estimates ranging from 3:1 to 9:1, depending on the frequency of cycling considered. In a meta-analysis of 10 studies enrolling 2,057 patients, 72% of rapid cyclers were women and 28% were men.[19] Some evidence indicates that compared with men who are bipolar, women suffer more depressive than manic episodes[20,21] and more often have mixed states.[22]

There is mixed opinion in the literature as to whether hypothyroidism, gonadal steroid effects, or antidepressant use predisposes a bipolar patient to rapid cycling. Available data show that women with bipolar disorder do not generally have mood fluctuations linked to the menstrual cycle. However, some women who do show this pattern may benefit from the use of oral contraceptives.[23]

The postpartum period is a vulnerable time for many women, especially those with a prior history of a postpartum episode. In one study of manic-depressive illness, the risk of cycling within the first 30 days postpartum was found to be 21% for women with manic episodes and 13% for women with depressive epsiodes.[24] Women with a previous postpartum episode had more than a 50% risk of reccurrence following a subsequent delivery.[25]

Many factors, including disruption of the sleep-wake cycle, dramatic shifts in the gonadal-steroid and thyroid axes, gradual discontinuation of medications (typically beginning about 4 weeks before childbirth), and dramatic changes in blood and fluid volume that occur at delivery, may raise the risk of postpartum episodes.[26-28]

Although gender differences in response to mood stabilizers have not been well studied, evidence suggests that rapid cyclers (who are more often women) are less likely to respond to lithium than are nonrapid cyclers.[29] Effective treatment of rapid cycling should maximize use of mood stabilizers, minimize use of antidepressants, and encourage stability in medications and lifestyle.

Even in some patients with severe depression, it is best to avoid tricyclic antidepressants (TCAs), which may induce mood switching and rapid cycling. Ongoing studies suggest that lamotrigine may be more effective than gabapentin in the treatment of rapid cyclers.[30-32] Some evidence supports the use of thyroxine (T_4) and nimodipine, a dihydropyridine calcium channel blocker (CCB), for rapid cycling.[33]

Bipolar illness is characterized by comorbidity, such as substance abuse, anxiety disorder, personality disorder, obsessive-compulsive disorder (OCD), and in children, attention deficit hyperactivity disorder (ADHD). The presence of comorbid conditions predicts poorer outcome and treatment response.[34]

The ECA data indicate that more than 60% of individuals with bipolar disorder meet lifetime criteria for a substance use disorder.[35] Similarly, the National Co-Morbidity Study,[36] which is a more recent epidemiologic survey, found an association with substance use disorder (odds ratio of 6:8). Although few data support the best treatment for these patients, valproate has shown favorable results in one open-label pilot study.[37]

Anxiety disorder often occurs in bipolar patients, with many samples showing 40% comorbidity with various anxiety disorders. It is likely that untreated panic disorder and other anxiety disorders may be associated with a worse course and prognosis of bipolar disorder. Valproic acid may be helpful in the treatment of concurrent panic disorder and bipolar disorder.[38,39]

Obsessive-compulsive disorder also appears to occur at a relatively high rate with bipolar disorder. An analysis of ECA data found OCD to be 18 times more likely to occur in patients with bipolar disorder than in the general population.[40] Caution is warranted in the treatment of comorbid OCD, as many medications used to treat OCD can precipitate mania; as many as 20% of patients may exhibit mania on antidepressants.[41]

Attention deficit hyperactivity disorder is another common comorbidity. One study reports that adult patients with bipolar disorder were significantly more likely to have childhood ADHD compared with patients with major depression.[42] Borderline personality disorder is also more commonly seen in children who go on to have bipolar disorder as adults. As with substance use, differential diagnosis is somewhat difficult, because symptoms of ADHD may also be features of a manic or hypomanic episode.

First-line treatments for ADHD, such as stimulants or antidepressants, are contraindicated in bipolar disorder and could exacerbate the course of the disease. Character pathology is also frequently present in bipolar patients. Personality traits are not easily distinguished from acute affective illness, and symptoms between bipolar disorder and several personality disorders overlap substantially.

Thus, personality disorder should be diagnosed in patients with bipolar disorder during times of stable affect to ensure accuracy.

In addition to its associated comorbidities, bipolar illness may represent many different illnesses with a similar phenotype. Clinically, observations show that bipolar illness may be either sporadic or familial, and its onset may be early or late, with many or few recurrences. Moreover, children born into families with existing affective disorders and alcohol abuse are more likely to be abused.

In the Stanley Foundation outpatient cohort, which studied more than 300 patients, a history of early physical or sexual abuse was a strong risk factor for the subsequent early manifestation of bipolar disorder. Patients with these histories had earlier onset of illness; faster cycling patterns, including more ultradian cycling; and increased risk of comorbidity with post-traumatic stress disorder (PTSD) and substance abuse.

Exposure to a chaotic environment during the neurodevelopmental years may contribute to the development of personality disorder intermixed with bipolar illness. A higher incidence of reported increasingly severe mania was associated with physical abuse, and a higher incidence of suicidality accompanied sexual abuse. In these cases, it is difficult to distinguish primary from secondary pathology.

Broad variability in the estimated prevalence of bipolar disorder in part relates to comorbidity. For example, clinicians often categorize bipolar patients with substance abuse as substance abusers. Bipolar patients appear to have a different pattern of substance abuse, however, more often bingeing, depending on their mood state. Many physicians minimize cyclothymia, viewing it simply as "life's ups and downs."

Patients who have suffered a traumatic brain injury or who have mental retardation or developmental disabilities are at increased risk for affective disorders, especially bipolar disorder, and typically have a mixed state disorder.[43] This population often has an atypical presentation of symptoms, leading to misdiagnosis and low prevalence rates of affective disorder in epidemiologic studies. In addition, symptoms of affective disorder may be misinterpreted as those of a psychotic disorder.[44]

NATURAL HISTORY AND COURSE

Following an initial episode, almost all patients with bipolar disorder have multiple recurrences and shorter symptom-free intervals with increasing age.[45] Rates of relapse and recurrence have been estimated at 80% to 90%.[46] The cumulative probability of recurrence has been estimated to be more than 50% during the first year of follow-up after an initial episode, about 70% to 90% by the end of 2 to 5 years.[46-48] Following recovery from a mood episode, patients may experience, on average, 0.6 episodes per year over a 5-year period.[42] Factors correlated with recurrence of a mood episode include substance abuse, psychotic features, and family history of mania or schizoaffective mania,[49] as well as age at onset, gender, premorbid psychosocial functioning, length of illness, and number of prior episodes.

Treatment with lithium may provide freedom from symptoms in approximately 33% of patients for 5 years after an initial episode, and combination treatment with benzodiazepines, and antipsychotics may provide an even greater degree of prophylaxis.[50] Although similar rates of efficacy have been reported for lithium and carbamazepine in maintenance therapy, methodology may be flawed.[51] In one trial, lithium used in combination with other medications was superior in preventing recurrence (28% lithium vs 47% carbamazepine) and was better tolerated. The converse was true for carbamazepine in atypical and schizoaffective patients.

SUBTYPES OF ILLNESS

Bipolar I disorder (mania and major depression) is the best studied subclass of bipolar illness, in terms of phenomenology, course, and outcome with and without treatment. Bipolar II disorder (hypomania and major depression) is increasingly recognized to be more common than previously thought, particularly in young people. Growing evidence indicates that bipolar II disorder also responds to mood stabilizers. A compound with mood stabilizing and superior antidepressant properties is desirable for treatment of bipolar I disorder but is not yet available.

Among patients with bipolar III disorder (cyclothymia), full-blown bipolar illness develops in about 30%. Some clinicians treat cyclothymia as they would a rapid-cycling bipolar disorder. Bipolar IV is antidepressant-induced hypomania. It is unclear whether this is an adverse effect of medication or the unmasking of a true underlying vulnerability for bipolar disorder, and thus may respond completely differently to treatment as compared to the "polar" disorder. Studies show the response to typical treatment with anticonvulsants may be poorer for induced mania than it is for standard mania.[52] The bipolar V disorder subtype is characterized by recurrent major depression

without hypomania and with a significant family history of bipolar disorder. Many patients with bipolar disorder, particularly of juvenile onset, begin their lifetime of mood problems with depression. Bipolar VI disorder (unipolar mania) is extremely uncommon. When it does occur, onset is usually after age 40. Thus, it is critical to rule out medical or neurologic causes.[53]

Bipolar disorder can present in many ways over a lifetime. Mixed states, rapid cycling, and psychosis may occur, as well as manic, hypomanic, and depressive episodes. Rapid cycling and psychotic features may represent a subtype of the disorder and may influence the efficacy of different medications during treatment. Over the course of a lifetime, monotherapy with a mood stabilizer may benefit only a minority of patients. In prospective outcome studies, less than half of patients sustained a good response to monotherapy treatment 4 years after an initial manic episode.[46]

> *"One small but placebo-controlled study with on-off, on-off confirmation has shown that patients with ultradian cycling respond well to nimodipine."*[58,59]

Rapid cycling is a specifier that may be applied to bipolar I disorder or bipolar II disorder. It is defined as the occurrence of 4 or more cycles per year[54] and occurs in 15% to 20% of bipolar patients,[55] and as many as 50% in some outpatient samples. Rapid cyclers are more likely to have associated hypothyroidism although whether this is an artifact of lithium treatment remains an issue.[55] In acute episodes, rapid cycling often shows a poorer response to lithium than to valproate or carbamazepine.[56] In contrast, classic bipolar I illness (3 or fewer cycles per year) responds better to lithium, although it may also respond to valproate and carbamazepine. Rapid cycling shows a 60% response rate to lithium compared with an 80% or better rate with pure mania.[54]

Lamotrigine may also have poorer efficacy in rapid cyclers than it does in nonrapid cyclers.[30] Ultra-rapid cycling consists of episodes that are days to weeks apart, or 4 episodes per month. In ultra-ultra or ultradian cycling, mood shifts occur in the same day for 4 days per week.[57] According to some estimates, the prevalence of ultra-rapid cycling is approximately 15% of all rapid-cycling bipolar patients, whereas ultradian rapid cycling has an approximate prevalence of 5%.[58] One small but placebo-controlled study with on-off, on-off confirmation has shown that patients with ultradian cycling respond well to nimodipine.[58,59]

Mixed episodes show a differential response to drug treatment. In a 15-month prospective trial, 54% of patients with pure mania and 87% with mixed mania had a marked response to valproate.[60] For the duration of the study, the prophylactic response for pure mania was 72% and for mixed mania 94%. Other treatment options have included thyroid hormone augmentation of a mood stabilizer at a dose to achieve 150% of normal thyroid function,[61] a combination of mood stabilizers, and clozapine as monotherapy or in combination with lithium or valproate.

For patients with depressive episodes, treatment options include supportive psychotherapy (psychoeducational, individual, family), use of mood-stabilizing agents, psychotherapy, antidepressant medication, and electroconvulsive therapy (ECT).[62] The treatment of bipolar depression has not been as well studied as that of bipolar mania or unipolar depression. Lithium is a first choice for bipolar depression,[63] although a full response may require 4 to 6 weeks.[62]

The role of antidepressants in bipolar depression is controversial, as a switch from depression to mania has been reported in 28% to 70% of patients taking TCAs and monoamine oxidase inhibitors.[10] A 1-year study found that a combination of lithium and bupropion had a lower switch rate (11%) than did lithium and desipramine (50%).[64] Switch rates for selective serotonin reuptake inhibitors (SSRIs), although not as well studied, may be lower than they are for TCAs. In 8 of 9 controlled trials reported in the literature, lithium was superior to placebo, and 3 trials show lithium equal to TCAs as treatment of bipolar I depression while using mood stabilizers, antidepressants, and ECT.

Three controlled trials that included patients with bipolar I and bipolar II depression found that carbamazepine was

more effective than placebo. No trials have evaluated valproate in bipolar depression. Electroconvulsive therapy was superior to TCAs in 5 of 7 studies and equivalent in 2 other studies. Five of 6 studies suggested that bipolar and unipolar depression respond equally well to ECT.[65] In 9 trials with 8 or more patients each, imipramine, bupropion, and fluoxetine were more effective than placebo, and mapropilitine, moclobemide, and bupropion were as effective as imipramine in bipolar depression. The overall efficacy of antidepressants for bipolar depression was 50% to 75%.[66] Not all patients in these trials were on mood stabilizers. Lamotrigine also has effects in bipolar depression.[31,32]

> *"Medications for bipolar disorder include those for treating an acute episode of depression or mania, those that prevent mood instability between episodes, and those that act adjunctively."*

III. TREATMENT MODALITIES

Medications for bipolar disorder include those for treating an acute episode of depression or mania, those that prevent mood instability between episodes, and those that act adjunctively. Lithium and perhaps other mood stabilizers can reduce the risk of suicide, and increase life expectancy, productivity, and functioning. Among patients who respond to mood stabilizers, 40% to 75% will achieve a reasonable occupational status and be able to live independently.[67,68] Lithium, valproate, and carbamazepine are widely used. Although they are considered standard treatment by many practicing physicians, the FDA approves only lithium and valproate for the treatment of bipolar illness. Carbamazepine, like many other pharmacologic treatments, is prescribed in off-label use. Alhough carbamazepine is not FDA approved for bipolar mania, the authors who reviewed 16 studies recommend it as a standard treatment option.[69]

LITHIUM

Efficacy. Lithium is a tried and tested medication, which is effective in acute mania, classic bipolar disorder,[70] and bipolar disorder with a mania/hypomania-depression-euthymia course.[71] Lithium is less effective in rapid cycling, mixed states, bipolar illness with comorbid substance abuse, and secondary bipolar disorder.[72] Although initial response rates to lithium were reported as 70% or higher, more recent research shows lower response rates of 25% to 50% for maintenance treatment, even when antidepressants and neuroleptics are used as adjuncts.[73-77]

In general, a previous good response, relatively few lifetime episodes, excellent interepisode recovery, positive family history of bipolar disorder with favorable response to lithium, pure but not severe mania, classic bipolar disorder with an episode sequence of mania-depression-euthymia, and adequate serum lithium levels predict a good response to lithium.[7,70,71,74] Multiple previous episodes, depression followed by mania, rapid cycling, mixed states, significant comorbidity with substance abuse, personality disorder, and lithium levels below 0.6 mmol/L may predict poor response to lithium.[72]

Discontinuation of long-term lithium therapy has been associated with a significant increase in the risk of recurrence. In one study, 50% of patients experienced recurrence within 6 months of discontinuation.[78] Patients who discontinue more slowly will relapse over a longer period of time, approximately 20 months. Discontinuation of lithium may be associated with an inordinately high increase—as high as 18-fold—in the risk of suicide compared with continued administration.[79]

A small percentage of patients who responded to lithium and then stopped taking it may not respond again when the drug is reinstituted.[39] Recent data suggest that lithium increases neurotrophic and neuroprotective effects and increases cell survival factors.[80] These actions may contribute to a reduction in the excess mortality from stroke and cardiovascular illness, which is often observed in patients with bipolar illness.

Pharmacology. Lithium has a narrow therapeutic index, optimally 0.8 mmol/L to 1.1 mmol/L and more broadly 0.5 mmol/L to 1.5 mmol/L. Above this range, the risk of adverse events and toxicity markedly increases; below it, the risk of relapse grows. Onset of effect usually takes 7 to 10 days. The half-life of lithium is 24 hours, time to steady

state is 5 days, and response occurs on average 18 days from initial treatment.[81-84] In one study,[85] lithium levels were observed to fluctuate with mood state, increasing with depression and decreasing with mania.

Adverse effects. Acute adverse effects of lithium can contribute to noncompliance in 30% to 50% of cases. Adverse effects include polydipsia, polyuria, weight gain, cognitive problems, tremor, gastrointestinal (GI) upset, acne, and hypothyroidism.[86] Rare but potentially serious side effects include arrhythmias, central nervous system (CNS) toxicity, and permanent cerebellar dysfunction from overdose. Due to lithium's narrow therapeutic range, changes in electrolyte and fluid balance can induce toxicity.

Many adverse effects of lithium, such as weight gain, acne, tremor, and cognitive dysfunction, may make it a less desirable choice for adolescents. Patients with developmental disabilities may have a lower seizure threshold, warranting greater caution when lithium is used. Moreover, this patient population may not report adverse effects or symptoms that would indicate imminent toxicity as readily as the general population.

Drug interactions. When lithium is administered concomitantly with other drugs (eg, carbamazepine, CCBs), the risk of neurotoxicity increases. Use with carbamazepine typically relates to an excessively rapid dose escalation of carbamazepine. Decreased blood levels may result when lithium is administered with CCBs and xanthine compounds, whereas increased levels may result when administered with thiazide diuretics and angiotensin-converting enzyme inhibitors.

Use in pregnancy. The risk of teratogenicity with lithium may be lower than previously reported.[87] The risk of Ebstein's cardiac anomaly was earlier reported to be 400 times normal for infants born to women taking lithium during pregnancy,[88] although a more recent review suggests the risk is much lower, 1.2 to 7.7 times normal or lower.[89] The teratogenic risk associated with lithium is likely comparable with that of valproate or carbamazepine, considering the association of the latter 2 drugs with neural tube defects.

VALPROATE

Efficacy. Valproate is an effective broad-spectrum alternative to lithium. It is effective in acute mania,[90] rapid cycling, mixed states, secondary bipolar disorder, and comorbid substance abuse and personality disorder.[72] It also has an important use in the prevention of relapse of postpartum depression. One report suggests that nonparoxysmal nocturnal abnormalities on electroencephalograph may predict a favorable response to valproate.[91]

Many clinicians increasingly choose valproate over lithium due to its broad spectrum of activity, shorter time to onset of action, larger serum therapeutic range, associated lack of need for blood level monitoring, relatively benign side effect profile, and apparent efficacy in maintenance treatment. Recently, data from a double-blind trial in bipolar disorder have been submitted to the FDA for approval of valproate in prophylaxis of bipolar disorder. In a placebo-controlled trial of acute mania, valproate was found to be as effective as lithium,[92] while acute episodes of mixed mania responded better to valproate than lithium.

Pharmacology. Although labeling suggests the use of doses up to 60 mg/kg/d, the literature supports the safe use of doses up to 100 mg/kg/d in selected patients.[93,94] Plasma levels should be maintained at 50 μg/mL to 125 μg/mL when lower doses are used, but may reach 200 μg/mL with higher doses. Treatment requires the adjustment of serum levels to achieve maximal efficacy and safety for the individual patient.

Valproate can have a rapid onset of action, within 3 days when an oral loading dose of 20 mg/kg/d is used. In a study of 19 patients with bipolar disorder, manic phase, a dose of 20 mg/kg/d in divided dosages for 5 days resulted in significant (greater than 50%) improvement in the Young Mania Rating Scale (YMRS) for 53% of patients, with minimal side effects.[95] Its half-life is 6 to 8 hours, and time to reach steady state is 1 to 2 days. A response is usually seen after 10 days. The valproate dose should be increased appropriately when carbamazepine is used concurrently, because carbamazepine induces hepatic metabolic enzymes.

Adverse effects. Common side effects of valproic acid include tremor, diarrhea, weight gain, alopecia, sedation, and benign elevation of liver transaminases. Serum levels greater than 100 μg/mL are associated with increased adverse effects,[96] including GI, sedative, and hematologic (thrombocytopenia, leukopenia) effects and hepatotoxicity. Some clinicians choose to monitor liver function in particular with polytherapy. Rare but potentially serious effects include leukopenia, thrombocytopenia, pancreatitis, and hepatotoxicity. Cognitive side effects may be less than those with lithium. For many patients, particularly women, adverse effects of alopecia and weight gain and concern about polycystic ovary syndrome may limit its use and

impair compliance. Alopecia can be avoided or ameliorated in some patients by augmenting selenium and zinc in the diet.

Use in pregnancy. The incidence of neural tube defects with valproate in the first trimester of pregnancy is about 2%.[95] Anecdotally, high doses of folate help prevent these defects.

Drug interactions. There are few drug interactions of clinical importance. Valproate inhibits the metabolic inactivation of the 10,11-epoxide of carbamazepine, thus contributing to undetected carbamazepine toxicity, because the 10,11-epoxide is not measured in routine assays. The dose of carbamazepine should accordingly be reduced when the two drugs are used in combination. Measurement of free serum valproic acid, rather than total valproic acid, may be more important in patients who are concurrently receiving carbamazepine. It is important to monitor for bleeding time and bruising when valproate is used together with any agent that alters platelets or blood clotting function. Continued monitoring of liver, hematologic, and serum levels is only needed after the first few weeks, if clinically indicated.[97] When valproate is used concurrently with lamotrigine, increased serum levels may be observed of either free valproic acid or lamotrigine, leading to increased incidence of their respective adverse effects.

> *"Elevations in liver function tests and decreases in white blood cell count, are not associated with significant clinical abnormality in most cases."*

CARBAMAZEPINE

Efficacy. Carbamazepine is effective for the treatment of acute mania, mixed state, or secondary bipolar disorder.[97] Although there are some data on its prophylactic efficacy, they are not as impressive as the evidence with lithium. It likely has antidepressant properties and is commonly used where lithium has failed.[99,100] Alhough carbamazepine is not FDA-approved for mania or bipolar illness in general, most authorities recommend it as a standard treatment option.[69]

A favorable response to carbamazepine is associated with a negative family history of bipolar illness, a nonrapid cycling course and lower T_4 levels during drug treatment. It appears more effective in depressions characterized by baseline increases in regional cerebral metabolism on positron emission tomography (PET) scan, particularly in the left insula, while the converse is true for the dihydropyridine L-type CCB nimodipine.[101]

Pharmacology. Carbamazepine has a narrow therapeutic index, and it is common practice to maintain a serum level of 4 μg/mL to 15 μg/mL, but it is more important to titrate the drug to a patient's side effect threshold. Its half-life is 24 to 48 hours, but with enzyme induction decreases substantially. Onset of action is within 1 week in mania and several weeks in depression, and the time to reach steady state is 4 to 10 days.

Carbamazepine induces its own metabolism by the liver, as well as that of many other drugs, through induction of the cytochrome P450 3A4 isoenzyme.[102] Concurrent administration of drugs that inhibit cytochrome P450 3A4 isoenzyme may elevate plasma levels of carbamazepine. Many clinicians hesitate to use carbamazepine because of this initial autoinduction and the resultant need for upward adjustment of dosage and its complex pharmacokinetic interactions.

Adverse effects. Compliance failure with carbamazepine is estimated to occur in 20% to 35% of cases, often due to adverse effects. These are dose-related and include sedation, cognitive impairment, diplopia, minor hematopoetic suppression, GI distress, weight gain, dizziness, benign elevations in liver enzymes, blurred vision, fatigue, nausea, ataxia, and hyponatremia. Rare but serious effects include exfoliative skin rashes (Stevens-Johnson syndrome), leukopenia, aplastic anemia, hepatic failure, and pancreatitis.[98,103] Anticonvulsant hypersensitivity reactions occur in 10% to 15% of epilepsy patients. Aplastic anemia occurs in approximately 6 out of a million patients.

Use in pregnancy. Neural tube defects have been reported when carbamazepine is used in the first trimester of pregnancy, and it is thought to have a higher teratogenic risk than lithium.[104] Craniofacial distortion may also occur.

Drug interactions. Use of carbamazepine with clozapine has been avoided because of the fear of increased risk for hematologic adverse effects. Use in combination with valproate, erythromycin (and its congeners), isoniazid, and some SSRIs and CCBs may lead to increased carbamazepine levels, whereas concurrent use with TCAs, theophylline, ibuprofen, warfarin, lamotrigine, and birth control pills may lower serum levels of these drugs.

Concurrent use with valproate may cause toxicity by increasing the plasma levels of the active 10,11-epoxide of carbamazepine by direct enzymatic competition. It can also increase plasma levels of carbamazepine and its epoxide metabolite by displacing them from their protein binding sites. In this circumstance, it may be useful to decrease carbamazepine dosage accordingly. The metabolism of oral contraceptives is increased with concurrent carbamazepine use, potentially resulting in unintended pregnancy. When cisapride is used concurrently, the levels of cisapride may fluctuate, and prolongation of the QT interval may result.

ELECTROCONVULSIVE THERAPY

Electroconvulsive therapy (ECT) is an effective treatment for acute depression in bipolar disorder. Bilateral ECT is also rapidly effective for acute mania, with about 80% of patients showing marked improvement.[105] Prospective studies, largely in unipolar depression, have considered it equally or more effective than drug therapy. In one study, 54% of medication-resistant patients acutely responded to ECT.[106] To maintain remission, ECT must be continued regularly in maintenance therapy or followed by a medication regimen. Although long-term cognitive side effects are typically less severe and common than thought, ECT remains unacceptable to many patients because of fear and cost.[107,108] Thus, it is not commonly used. Electroconvulsive therapy is thought to be relatively safe for use in pregnancy and in the presence of concurrent medical conditions, such as acute myocardial infarction. Effectiveness in long-term prophylaxis has not been demonstrated, although controlled studies are in progress.

COMPARISON OF LITHIUM, CARBAMAZEPINE, AND VALPROATE

Lithium, valproate, and placebo were compared in the treatment of acute mania in a double-blind, randomized, parallel group study enrolling 179 acutely manic, hospitalized patients.[92] After 21 days of treatment with valproate, lithium, or placebo, 30%, 33%, and 51% of patients, respectively, discontinued their medication due to lack of efficacy. The proportion of patients in each treatment arm showing 50% improvement was 48%, 49%, and 25%, respectively. The limited extent of measurable improvement rather than remission suggests the importance of using combination drug therapies in patients refractory to monotherapy.

The efficacy of prophylactic treatment with lithium, carbamazepine, valproate, and combinations thereof was evaluated in two related studies. Lithium, carbamazepine, and the combination were compared in a double-blind study of 52 outpatients with bipolar illness.[73] Patients were randomly assigned to 1 year of treatment with lithium or carbamazepine, followed by 1 year of treatment on the alternative drug, and then 1 year on combination therapy with lithium and carbamazepine. The percentage of evaluable patients who had marked or moderate improvement on the Clinical Global Impressions (CGI) scale was 33% on lithium, 31% on carbamazepine, and 55% on combination treatment.

In a follow-up study,[109] those who in the first study had responded inadequately to lithium received valproate and lithium in combination for 1 additional year, and then subsequently 1 year of triple therapy. Of these patients, 33% showed a moderate to marked improvement while receiving valproate plus lithium, and 3 of 7 responded to triple therapy. Results from these 2 studies show that patients refractory to lithium and carbamazepine may benefit from prophylactic combination treatment with valproate and lithium or triple therapy.

Three other double-blind, randomized trials have compared lithium and carbamazepine in the treatment of bipolar illness.[110-112] Results of 2 of these studies.[111,112] show the two treatments to be equivalent, with approximately a 60% response rate, while another study[110] showed better results for lithium, 61% vs 24%.

NEED FOR MONITORING

For many clinicians practicing in a community setting, use of mood-stabilizing drugs, either alone or in combination, often involves regular monitoring of drug levels, blood cell counts, and liver function. The literature, however, shows little evidence to support this practice. Elevations in liver function tests and decreases in white blood cell (WBC) count, which are often observed, are not associated with significant clinical abnormality in most cases.

For many patients, the cost of routine monitoring is a limiting issue, forcing them to choose between paying for a

month's supply of drug or blood tests. For patients participating in managed care plans, mental health benefits are often established at a fixed amount. In such circumstances, the cost of routine monitoring represents a portion of the total benefit allowed, reducing the benefits available for other mental health services.

In contrast, routine monitoring may often be necessary for special patients who are unable to verbalize adverse effects they may be experiencing. It may also lower the patient's threshold for acceptance of the risks associated with these drugs. Adequate informed consent requires advising the patient of the possibility of serious adverse effects, even with routine monitoring, which may not detect all cases of impending catastrophic events.

Blood counts. While a transient drop in WBC count is observed in approximately 12% of patients taking carbamazepine, there is no evidence that this presages full-blown bone marrow suppression. The absolute neutrophil count is a more critical measure of hematologic status than the WBC count. Often, bone marrow suppression is not predicted by any laboratory finding, and it is rare, occurring in 6 of every 1 million treated patients.

Some investigators have observed the occurrence of a viral-like illness with myalgia and arthralgia before onset, coupled with a low reticulocyte count, as predictive of a serious effect on bone marrow. For many clinicians, abnormal laboratory values have more significance when considered representative of a trend toward a greater abnormality rather than independent values. In addition, abnormal trends are best evaluated in the context of clinical findings (eg, fever, sore throat, persistent bruising). Some investigators consider laboratory testing unnecessary in the absence of any such signs or symptoms.

> ***"The absolute neutrophil count is a more critical measure of hematologic status than the WBC count."***

Liver function tests. In many studies, approximately 25% to 75% of patients have experienced elevations in 1 or more liver function tests (eg, aspartate aminotransferase, alanine aminotransferase, alkaline phosphatase). Often, such elevations indicate an induction of hepatic enzymes involved with drug metabolism and not hepatotoxicity. The clinical benefits of continuing an effective treatment must be weighed against the risk, as yet unproven, of liver enzyme elevations leading to hepatotoxicity.

For many clinicians, elevations in liver enzymes of up to 3 to 4 times normal are not cause for concern, particularly if albumin, protein, and clotting factors are unaffected, indicating adequate liver function. As with blood monitoring, many investigators recommend measuring laboratory tests if there is clinical evidence of hepatotoxicity (eg, persistent nausea, jaundice, joint pain, or severe rash). Consultation with a hepatologist may be indicated.

Blood urea nitrogen and creatinine. For patients on lithium, periodic monitoring of blood urea nitrogen (BUN) and creatinine levels and creatinine clearance may be useful. Once-yearly testing may be adequate. Such problems are usually seen in patients who have been receiving lithium long-term and who have had steadily increasing creatinine levels over time. If the patient has had an otherwise favorable response to lithium but has significantly reduced renal function, consultation with a nephrologist may be appropriate. When used with lithium, amiloride may have a protective impact on long-term renal function, which may help reduce the potential for nephrogenic diabetes insipidus.[113]

Blood ammonia. In a rare adverse effect associated with anticonvulsants, blood ammonia levels may increase. As with blood and liver function tests, abnormalities are best interpreted while considering the clinical signs and symptoms of illness. A caveat in interpreting blood ammonia levels is that testing is technically difficult to do, is not routine for many testing laboratories, and is often done improperly. To obtain an accurate result, the sample must be iced immediately and assayed within minutes after it is collected. In patients receiving valproate, trough levels of free valproic acid may be a more useful measure to correlate with the clinical picture.

IV. NONSTANDARD TREATMENTS

LAMOTRIGINE

Lamotrigine's mechanism of action is thought to be related to inhibited recovery of voltage-activated sodium channels (phenytoin, carbamazepine) and the resultant inhibition of neurotransmitter release (glutamate, aspartate, acetylcholine, γ–aminobutyric acid [GABA]), which sodium influx mediates. Since lamotrigine is effective in absence epilepsy, it may act by different mechanisms than does carbamazepine, which can exacerbate absence epilepsy.

Lamotrigine has shown promise in bipolar depression and rapid cycling bipolar disorder in open studies.[113-117] A placebo-controlled crossover trial compared the efficacy of 6 weeks' administration of lamotrigine, gabapentin, and placebo as monotherapy in highly refractory patients with affective disorder. The CGI score showed marked to moderate improvement in 52% of patients receiving lamotrigine, compared with 27% taking gabapentin and 23% taking placebo.[118]

The characteristics of patients who showed preferential response to lamotrigine included male gender, bipolar (rather than unipolar) illness, and fewer previous drug trials and hospitalizations for depression. Both rapid and nonrapid cyclers were found among the responders. Some investigators have observed, however, that rapid cyclers may experience a slight acceleration of mania while on lamotrigine.

A double-blind randomized study has demonstrated the efficacy of lamotrigine in bipolar depression with doses of 50 mg/d and 200 mg/d; both were more effective than placebo.[31] Lamotrigine's effectiveness in mania remains under investigation. In uncontrolled trials, mixed mania patients unresponsive to combinations of standard mood stabilizers did respond to lamotrigine monotherapy and lamotrigine in combination with other mood stabilizers and antipsychotic medications.[119] In a study of 67 patients who had refractory bipolar disorder and were taking a concurrent mood stabilizer and antipsychotic medication, 82% of those with depressive symptoms and 76% of those with manic symptoms had moderate or marked improvement with lamotrigine treatment.[120,121]

Dosage should be initiated with a low dose and slowly titrated upward to minimize the occurrence of adverse effects, especially serious rash. When lamotrigine is used in combination with valproate, one half the recommended dose should be used. When used in combination with carbamazepine, lamotrigine can be doubled in dose. Adverse effects include dizziness, tremor, ataxia, diplopia, headache, and GI upset. Lamotrigine causes a macular, papular, pruritic rash in approximately 5% to 10% of patients; this effect may be related to the rapidity of dose escalation. Use of slow increases appears to decrease the observed frequency of rash. Stevens-Johnson or Lydell's syndrome, serious and potentially life-threatening rashes, may develop in approximately 1 in 100 children and 1 in 300 adults.

GABAPENTIN

Gabapentin inhibits branched-chain amino acid transferase and possibly the synthesis of glutamate from branched chain amino acids in the brain. As a result, brain and spinal fluid levels of GABA are increased. In a 6-week, double-blind randomized trial of gabapentin monotherapy, a 27% response rate to gabapentin, in doses up to 4800 mg/d, was observed in patients with refractory affective disorder, not different from the 23% rate in patients taking placebo.[32] At baseline, patients who responded to gabapentin were younger and less overweight, and they had shorter duration of illness.

On the other hand, when gabapentin was used in combination therapy or as add-on therapy, at a mean dose of 1050+640 mg/d, higher response rates (53%) were typically observed.[122] In a case series, 18 of 28 patients with bipolar disorder who received gabapentin (average dose, 539 mg/d) in combination with a mood stabilizer and antipsychotic medication showed moderate to marked improvement.[123] These findings potentially support the clinical use of gabapentin as adjunctive therapy, but not monotherapy, in bipolar illness. Gabapentin may also have some efficacy in primary syndromes of anxiety, social phobia, pain, and tremor.

Gabapentin has few pharmacokinetic interactions with other drugs and has an extraordinarily high range of tolerability. As its dosage increases, absorption decreases, and the excess is excreted unchanged. Gabapentin should be given in divided doses, since a large single dose may block absorption. The optimal dose and blood levels for acute treatment and prophylaxis require further exploration. The principle adverse effects include somnolence, fatigue, ataxia, dizziness, and GI upset.

TOPIRAMATE

Topiramate may work through inhibition of the voltage-gated sodium channel and blockade of kainate and the AMPA (alpha-amino-3-hydroxy-5 methyl-4 isoxazole propionic acid) subtype of the glutamate receptor. It may also enhance GABA receptor actions. The role of topiramate in monotherapy is questionable. In a pilot study of 54 patients from the Stanley Network Outpatient Study, topiramate as an open add-on agent showed some efficacy in the treatment of mania and cycling, but had no acute antidepressive effect.[124] Patients who were cycling, however, had some improvement in their depression. As in the neurologic literature, dose-related weight loss was observed.

In 3 other case series, patients have shown similar response rates and degrees of weight loss. Topiramate was primarily used as adjunctive therapy. In this capacity, it may have a role in reducing the weight gain often associated with other psychotropic drugs. The dose should be titrated slowly. Principal adverse effects include weight loss, dizziness, tremor, ataxia, headache, fatigue, GI upset, renal calculi, and cognitive difficulties (eg, confusion, word finding, speech difficulties).

TIAGABINE

Tiagabine prolongs the action of GABA by increasing brain GABA levels by inhibiting the high-afffinity uptake systems in presynaptic neurons and glia. In an open trial, tiagabine showed no pronounced effect in reducing manic symptoms over a 2-week observation period in 8 acutely manic patients; one patient experienced a seizure.[125] Thus, particular care should be taken with the use of this agent, as evidence of its efficacy in bipolar illness is not available. The principal adverse effects associated with tiagabine in seizure patients include dizziness, asthenia, headache, somnolence, ataxia, fatigue, poor concentration, abnormal thinking, depression, nervousness, and tremor.

THYROID AUGMENTATION

Triiodothyronine (T_3) or thyroxine (T_4) can be used to enhance a partial response or accelerate the onset of clinical improvement. T_3 has shown efficacy in refractory unipolar depression, both alone and in combination with T_4.[126,127] Regular dose (23-37 μg) T_3 augmentation may be useful, in some cases providing benefit equal to that of lithium augmentation. In rapid cycling[128,129] and refractory depression,[127] some investigators recommend T_4 doses of 400 μg to 500 μg to achieve a free thyroxine index of 150% of normal coupled with TSH suppression.[128,129]

Most clinicians use high-dose thyroid augmentation late in treatment of refractory illness. A trial is currently evaluating long-term high-dose T_4 and T_3 treatment versus placebo in long-term prophylaxis of bipolar illness.[131] Acute responses to these agents may be greater in women than in men; in one report, 70% of women versus 20% of men responded to T_4, and 44% of women versus 10% of men responded to T_3.[132]

Adverse effects associated with long-term treatment include sweating attacks and cardiac symptoms. Osteoporosis and osteopenia may occur in patients concomitantly taking anticonvulsants, due to interference with vitamin D metabolism. This is more true in patients with mental retardation or developmental disabilities, who are often receiving long-term or lifetime treatment.[133] It may be advisable to obtain a baseline dual energy X-ray absorptiometry bone scan. Calcium replacements, regular exercise, and vitamin D supplementation may be useful to increase calcium deposition. Cholesterol-lowering drugs also increase bone deposition and may help prevent osteoporosis. Accurate measurement of levels of free serum T_4 requires an equilibrium dialysis method, because of extensive protein binding by anticonvulsant medications.

REPEATED TRANSCRANIAL MAGNETIC STIMULATION

Repeated transcranial magnetic stimulation (rTMS) may offer new possibilities in the treatment of affective disorders. Although it has been studied mostly for refractory unipolar depression, some data suggest it may also ultimately have a role in bipolar illness. It allows delivery of different frequencies of focal brain stimulation, depotentiating areas of hyperactivity with low frequencies, while normalizing areas of hypoactivity with higher frequencies. Unlike ECT, it is not associated with significant cognitive impairment, and it is well tolerated. With further research to establish optimal parameters of use (eg, location, frequency), rTMS may become a recognized treatment, although there is no clear consensus at this time.

CALCIUM CHANNEL BLOCKERS

These are discussed in greater detail in Section V.

V. ADJUNCTIVE TREATMENTS

BENZODIAZEPINES

Generally, high potency benzodiazepines (lorazepam and clonazepam) are used in acute mania to decrease agitation and as short-term treatment for insomnia. There is some evidence from controlled studies that the benzodiazepines lorazepam and clonazepam are effective as primary antimanic agents; lorazepam may be superior,[136] although this conclusion remains controversial. There is growing clinical experience on their efficacy as adjunctive treatment when used with mood stabilizers to treat acute mania[92] and to reduce anxiety and agitation during prophylaxis. Commonly, the dose is slowly tapered and then discontinued within 2 to 3 weeks of achieving symptom control in mania or depression. Risks associated with benzodiazepines include dependence, paradoxical excitation, disinhibition and decreased cognitive ability (especially in people with developmental disabilities).

TYPICAL ANTIPSYCHOTICS

Antipsychotic medications are used for psychotic symptoms of bipolar illness and occasionally for severe agitation that is unresponsive to benzodiazepines. Many clinicians erroneously consider the efficacy of an antipsychotic as diagnostic of a schizophrenic or schizoaffective process. Intermittent or long-term use of antipsychotics may be necessary for psychotic symptoms that have not responded adequately to standard mood-stabilizing agents.[63,137] There is less evidence supporting their use as prophylactic agents. Because patients with bipolar disorder are at increased risk for movement disorders, they often experience acute extrapyramidal side effects and a 20% to 40% rate of tardive dyskinesia. In some series but not others, typical neuroleptics can provoke or maintain depression in patients with bipolar disorder.[138]

> *"Repeated transcranial magnetic stimulation (rTMS) may offer new possibilities in the treatment of affective disorders."*

ATYPICAL ANTIPSYCHOTICS

The FDA has recently approved olanzapine for the treatment of acute mania. The olanzapine HGEH Study Group conducted a double-blind, placebo-controlled trial[5,35] and reported that olanzapine, used at doses of 10 mg/d to 20 mg/d for 21 days, resulted in significantly greater mean improvement in YMRS scores than did placebo. Reductions in the YMRS score of at least 50% were observed for 48% of patients taking olanzapine versus 24% of those receiving placebo.[139]

Adverse effects associated with olanzapine include weight gain, somnolence, dizziness, and dry mouth. In one study of 9 patients, olanzapine was also evaluated as adjunctive treatment in mixed states.[139] Patients had bipolar I disorder and failed to respond to mood stabilizers either alone or in combination with neuroleptics. Highly significant improvements were noted on measures of CGI, Brief Psychiatric Rating Scale, and Global Assessment of Functioning ($P<0.001$, respectively). Some clinicians have observed that women respond better to olanzapine than men do.

Clozapine is effective for refractory bipolar illness, particularly in patients with dysphoric mania and rapid cycling.[140-142] Problems associated with clozapine include seizures, weight gain, and a 2% to 4% incidence of agranulocytosis, which necessitates regular WBC monitoring. One study of note has evaluated the efficacy of risperidone, 2.8 mg/d for 6 months, as adjunctive treatment in 12 outpatients with bipolar disorder experiencing breakthrough episodes. Results showed that of 8 patients completing the study, 4 showed improvement in CGI scores, supporting the use of this drug in this subgroup of bipolar patients.[143] One report evaluated quetiapine in patients with bipolar I disorder who were nonresponsive to or intolerant of standard treatments.[144] On a retrospective chart review, 2 out of 6 patients showed moderate to marked improvement on the CGI scale. The main side effect was sedation.

ANTIDEPRESSANTS

Although a number of standard antidepressants appear to be effective treatment for bipolar depression, some classes of these drugs, especially the TCAs, can induce mania and accelerate cycling in some bipolar patients.[145,146] For these reasons, many clinicians believe antidepressants may interfere with eventual mood stabilization and thus prefer to use them as adjunctive agents with mood stabilizers, rather than as first-line therapy or monotherapy.

Bupropion, an antidepressant with a novel mechanism, acts through dopamine and noradrenergic systems. It appears to be an effective treatment for bipolar depression and may be less likely to induce switching into hypomania or accelerate cycling than desipramine is.[147] The switch rate following use of SSRIs may also be relatively low. Bupropion should be prescribed cautiously in patients with already reduced seizure threshold (eg, those with mental retardation).

CALCIUM CHANNEL BLOCKERS

RATIONALE

Calcium channel blockers were first used in psychiatry in the early 1980s. At that time, lithium was shown to induce early elevation of parathyroid hormone secretion, which causes renal retention of calcium. It was observed that in patients taking lithium for at least 2 years, hyperparathyroidism, occasionally of clinical significance, commonly occurred. It was hypothesized that lithium may interfere with intracellular calcium signaling and hypothesis that other drugs interfering with calcium signaling could exert antimanic effects.

> *"Among CCBs, verapamil, diltiazem, and nimodipine have been studied in bipolar disorder."*

Individuals who have bipolar depression and mania but not unipolar depression or euthymia have indeed been observed to have elevated intracellular calcium ion signaling.[148] This led to investigation of the use of CCBs in bipolar disorder. Some anticonvulsant drugs with antimanic properties (eg, carbamazepine) and TCAs have confirmed or possible calcium antagonist properties.[122,148-154] Some CCBs, such as nimodipine and verapamil, have been shown to be effective for bipolar disorder.

PHARMACOLOGY OF CCBS

Chemistry. The chemical structure of CCBs is diverse and represents four different chemical classes. While verapamil is representative of the phenylalkylamine class, nimodipine, isradipine, amlodipine, nicardipine, nifedipine, and felodipine are of the dihydropyridine class. Bepridil is a diarylaminopropylamine ether, and dialtiazem is a benzothiazepine.[155]

Lipophilicity. Calcium channel blockers have varying lipophilicity. Nisoldipine is the least lipophilic and is not believed to cross the blood-brain barrier. Nimodipine is very lipophilic, while verapamil and diltiazem are of intermediate lipophilicity. Nimodipine appears to have unique benefits because of its lipophilicity, which permits penetration of the blood-brain barrier and enables activity at doses that have little or no effects on blood pressure and heart rate. Other CCBs typically require doses that have a higher propensity for circulatory effects (eg, reduced arterial blood pressure and heart rate).

Mechanism of action. Free intracellular calcium ion concentration is increased through 3 mechanisms. Firstly, voltage-sensitive calcium channels open in response to depolarization of the membrane. Secondly, receptor-operated channels may increase calcium influx. Receptor activation also can induce the hydrolysis of phosphatidylinositol bisphosphate in the membrane. Inositol triphosphate, a second messenger produced by this reaction, signals release of calcium from intracellular stores. Actions on voltage-dependent calcium channels seem to mediate the neuronal effects of CCBs. This inhibition occurs at significantly lower concentrations than are required to interfere with the release of intracellular calcium or to block receptor-operated channels and occurs in hyperactive cells more than in normal cells.

Three main types of voltage-dependent calcium channels, the L-type, T-type, and N-type, have been described, based on conductance and sensitivity to voltage. The L-type chan-

TABLE 1 PHARMACOKINETICS OF CALCIUM CHANNEL BLOCKING AGENTS

DRUG	BIOAVAILABILITY (%)	HALF-LIFE (HOURS)	PROTEIN BINDING (%)	VOLUME OF DISTRIBUTION (L/KG)	URINARY EXCRETION OF UNCHANGED DRUG (%)	ACTIVE METABOLITES
AMLODIPINE	64	34	97	21	—	NO
BEPRIDIL	59	33	99	8	<1	YES
DILTIAZEM	40	3-5	70-80	3.3-5.1	2-4	YES
FELODIPINE	13-16	10-18	99	0.6-1.5	0	NO
ISRADIPINE	15-24	8	95	3	0	NO
NICARDIPINE	35	9	95	0.6	<1	NO
NIFEDIPINE	40-70	2-5	92-99	0.6-1.5	<1	NO
NIMODIPINE*	13	5	95	0.9-2.3	0.1	NO
VERAPAMIL	20-35	4.5-12	90	4.5-7	3-4	YES

*BIOAVAILABILITY MAY BE REDUCED TO 6%-8% WHEN TAKEN ON AN EMPTY STOMACH.

nel, also called the slow channel, is especially sensitive to dihydropyridine CCBs.[155] Depolarization of the neuronal cell increases calcium levels and activates intracellular enzymes. Activation of cyclic AMP, which is required for the biosynthesis of neurotransmitters (eg, serotonin, norepinephrine, acetylcholine), is a calcium-dependent process, and interference with this process eventually leads to decreased neurotransmitter release.

By this mechanism, abnormal calcium levels may affect the noradrenaline/serotonin system, which seems to be involved in mania and depression.[149] Other antimanic treatments, such as lithium and some anticonvulsants, have also demonstrated inhibitory effects on CNS calcium-dependent systems, specifically via calcium channels. L-type calcium channels have an important role in long-term potentiation of the amygdala, which is thought to be a key brain structure for modulation of affect.

Effects on the vascular system. All CCBs relax arterial smooth muscle but have little effect on most venous beds. In the heart, CCBs induce a negative inotropic effect, decrease coronary vascular resistance, and increase coronary blood flow. With the dihydropyridine class, a greater degree of peripheral vasodilation is observed, accompanied by a sufficient increase in sympathetic tone to overcome the negative inotropic effect.

Although the dihydropyridines lack antiarrhythmic properties, they have antihypertensive and antianginal properties. Nicardipine and felodipine may have a lower degree of negative inotropy than other dihydropyridine calcium antagonists. Because of its high lipid solubility, nimodipine is the agent of choice to relax the cerebral vasculature. It is used primarily to attempt the prevention of vasospasm after subarachnoid hemorrhage.[155] In contrast to the dihydropyridines, diltiazem and verapamil have cardiac effects and are used to treat supraventricular arrhythmias.

Pharmacokinetics. As a class, CCBs are nearly completely absorbed after oral administration, but the extent that their bioavailability is reduced dependis on the specific drug, due to first-pass hepatic metabolism. All are bound to plasma proteins to a significant extent (70%–98%), and they have short half-lives. Except for amlodipine, which has a longer half-life, CCBs require frequent dosing. While metabolites of diltiazem and verapamil have some appreciable biologic activity, the metabolites of the dihydropyridines are inactive or weakly active.[131] Table 1 summarizes the pharmacokinetic properties of CCBs.[156]

CLINICAL USE

Track record of efficacy. Among CCBs, verapamil, diltiazem, and nimodipine have been studied in bipolar disorder. Data from most clinical trials in acute mania have been positive.[157] Studies of CCBs as maintenance therapy have generally been placebo crossover studies of a few months' duration, enrolling small numbers of patients. Verapamil may be particularly useful in bipolar patients who have previously responded to lithium but are unable to tolerate its side effects or have become pregnant. As monotherapy, verapamil appears to be relatively inefficacious in refractory illness. The National Institutes of Mental Health is conducting a randomized, double-blind, multicenter trial of verapamil in bipolar disorder.

Aside from open case series, only one controlled study has shown efficacy of nimodipine as an antimanic and mood - stabilizing agent.[58,59] Compared with other drugs, nimodipine has an important advantage in that it is highly lipophilic, has a high affinity for the CNS, and has minimal peripheral vascular effects. Available data suggest that nimodipine may be useful in some illness refractory to lithium. Such patients tend to be rapid cyclers, with dysphoria, ultra-rapid and ultradian cycling. Alternatively, these patients may also be treated with carbamazepine or valproate as a primary agent, with a CCB, neuroleptic, or benzodiazepine added as an adjunctive agent as indicated. Diltiazem has been studied in acute mania and demonstrated a brief positive effect when used with adjunctive agents.[158]

> *"Nimodipine is one of the few drugs found to increase the cerebrospinal fluid (CSF) levels of somatostatin.[155]"*

There is some evidence that dihydropyridine L-type CCBs may be effective as antimanic agents, with efficacy comparable with verapamil, a phenylalkylamine. In addition, these types may be more effective than verapamil in the treatment of depression and rapid cycling.[59,159] Three patients who attempted to change from nimodipine to verapamil were unsuccessful, although some who responded to nimodipine were successfully transitioned to another dihydropyridine L-type CCB, isradipine.

Anecdotal observation suggests that amlodipine, another dihydropyridine, may share the same positive psychotropic profile of effects as nimodipine. These observations suggest that some rapid and ultradian cycling patients may show important degrees of response to dihydropyridine CCBs.

Calcium channel blockers can often substitute for lithium[159] and appear to have a much more benign side effect profile, because they are less sensitive to fluid and electrolyte balance; do not cause tremors, kidney, or thyroid problems; are well tolerated, with few GI and other side effects; and are weight neutral. Nimodipine is one of the few drugs found to increase the cerebrospinal fluid (CSF) levels of somatostatin.[160] This finding may also explain the relative lack of cognitive dysfunction observed with nimodipine as compared with lithium or anticonvulsants, such as carbamazepine, which lowers CSF somatostatin. Low CSF somatostatin levels have been associated with memory deficits in delirium, and some neuropsychological disorders including Parkinson's disease, Huntington's chorea, Alzheimer's disease, multiple sclerosis, Cushing's disease, and depression.

There are several reports in the literature on the use of nimodipine for bipolar disorder.[58,140,161-165] In one open trial, 6 patients with acute mania were successfully treated with nimodipine with no cardiovascular side effects; 3 patients also required droperidol to control excitement. In the another trial, 3 patients with ultra-rapid cycling and 1 with rapid cycling bipolar disorder, all refractory to lithium, had some response, and 4 patients with rapid cycling did not respond to nimodipine. Of the rapid-cycling patients, 2 required adjunctive carbamazepine treatment. In a case report, 2 rapid cycling patients were successfully treated with nimodipine.

A preliminary open study directly compared lithium and nimodipine in rapid cycling bipolar disorder.[140] In this study, 12 patients received lithium, nimodipine (30 mg tid), or both for 6 months each, in a crossover design. The combination was found to be more effective than either agent alone. These data suggest nimodipine may be a therapeutic option in some patients with bipolar disorder, including that refractory to lithium. In contrast, bipolar

disorder refractory to lithium typically fails to respond to verapamil. Nimodipine's efficacy and its apparent improved safety profile may put it at an advantage in the treatment of refractory bipolar disorder, although this remains to be directly demonstrated.

There has also been one trial of the successful use of nimodipine in 10 patients with depression.[166] In another case report, combination treatment with nimodipine 270 mg/d and lithium 900 mg/d was found beneficial in treating a prolonged manic episode in a 42-year-old female patient with bipolar I manic syndrome. This patient suffered from depressive episodes lasting 3 to 4 months, despite treatment, and from annual severe manic episodes lasting 3 to 5 months.

The patient's illness was being treated unsatisfactorily with lithium 900 mg/d and neuroleptics (haloperidol, benperidol, thioridazine). Replacement of the neuroleptic component with nimodipine, titrated up to 270 mg/d, led to continuous improvement over 2 weeks and discharge after 18 days. Lithium blood levels remained constant throughout nimodipine treatment, and side effects were absent. Discontinuation of nimodipine led to rehospitalization within 2 months.[163]

Position emission tomography scanning found that patients with bipolar illness may respond differentially to carbamazepine and nimodipine.[101] Baseline regional cerebral glucose metabolism and CGI were measured to determine if there were any differences between responders to these 2 drugs and healthy controls. Patients who responded to carbamazepine had baseline left insular hypermetabolism compared with healthy controls and nonresponders, and the degree of carbamazepine response correlated with baseline paralimbic and prefrontal hypermetabolism.

Carbamazepine decreased widespread metabolism, and the degree of decrease in the left insula correlated with response. In contrast, patients who responded to nimodipine had hypometabolism at baseline, including in the left insula, correlated with the degree of nimodipine response. Many patients in this study were rapid-cycling bipolar II patients. One study is underway to similarly evaluate valproate and lithium.[101]

Track record of side effects. Calcium channel blockers are fairly well tolerated by most patients, especially compared with standard drugs used to treat bipolar illness. Typically, there is no need for routine monitoring and no associated weight gain. The most common side effects are due to excessive vasodilatation and include dizziness, hypotension, headache, flushing, digital dysesthesia, and nausea. Patients may also experience constipation, peripheral edema, coughing, wheezing and pulmonary edema. Peripheral edema is more common with verapamil and occurs to a lesser extent with diltiazem and nifedipine. It is infrequently observed with nimodipine. Verapamil often causes constipation and headaches at higher doses.

Many clinicians have noted that in bipolar patients, occasional extrapyramidal side effects (ie, stiffness, tremor) are observed during treatment with flumerazine, verapamil, or amlodipine, possibly occurring through interference with the calcium-dependent dopamine D2 receptor. On the other hand, when used as adjunctive agents with neuroleptics, CCBs may reduce symptoms of tardive dyskinesia through blunting of a hyperactive dopamine signal in movement centers of the brain.

Achievement of this benefit typically requires high doses (eg, 480 mg/d of verapamil). Nimodipine may be associated with fewer adverse effects than other CCBs. The most common side effect observed with nimodipine is hypotension, occurring at an incidence of 4.4%. In a survey of 421 patients, this was reported to occur mainly in subjects with hypertension.[166] Nimodipine does not appreciably interact with either carbamazepine or valproate.

Titration of calcium channel blockers. Some investigators experienced in the use of nimodipine recommend the following titration schedule:

Start at 90 mg dosage, then double this in 10-14 days. After another 10 days, increase the dosage to 270 mg daily. Continue on this dose for several weeks and evaluate efficacy. Then increase the dose further incrementally, to 360 mg, 540 mg, and 720 mg daily, while evaluating clinical improvement. Many clinicians find that one-third to one-half of patients who had responded only partially will respond at the higher dose levels, 360 mg to 720 mg. Those who fail to respond initially often do not respond to higher doses, however. When using the higher doses, it may be advisable to monitor irregularity in heart rate or blood pressure, obtaining an ECG as indicated. Presentation with exertional dyspnea often indicates a potentially excessive dosage.

Interactions with other mood stabilizers. Calcium channel blockers are inhibitors of the cytochrome P450 3A4 isoenzyme, and concurrent administration with carbamazepine may elevate free carbamazepine and free carbamazepine 10,11-epoxide levels substantially and induce neurotoxicity. Concurrent administration of verapamil and lithium may

act synergistically on the heart and produce bradycardia. Safe use of lithium and verapamil together may require monitoring of vital signs, with adjustment of the lithium dose downward or slower titration of the verapamil dose.

Relatively high doses of verapamil are needed for sufficient antimanic effect, because of extensive first-pass metabolism. Phenytoin toxicity has occurred when it is used with nimodipine, and plasma phenytoin levels should be monitored. Phenytoin, carbamazepine, and phenobarbital have been shown to decrease plasma nimodipine concentrations, and concomitant use may require increased doses of nimodipine. Valproic acid and cimetidine were shown to increase nimodipine plasma concentrations via enzyme inhibition, and concomitant use may require lower doses of nimodipine. Verapamil appears to be safer than mood-stabilizing agents, lithium, valproate, and carbamazepine, during pregnancy.

COMBINATION DRUG THERAPY

In animal models, it has been observed that the development of tolerance is slower when more effective drugs are used, at higher doses (rather than minimally effective doses), and earlier in the disease process. In addition, the development of tolerance is minimized when treatment is escalated in the face of breakthrough episodes, when several drugs are used in common, and when drugs with different mechanisms of action, not showing cross-tolerance, are used together. Some of these same principles may be applicable and useful clinically. In the clinical arena, many complex syndromes, such as AIDS, cancer and congestive heart failure, require multiple drugs in combination for effective treatment. In particular, use of a new drug with a new mechanism of action may be highly effective, especially when dose escalation is not. With this approach, it may be possible to use lower doses, with less toxicity resulting, and a more persistent therapeutic effect. Fewer side effects may increase compliance. Perhaps the strongest rationale suggesting this approach is patient need. In the absence of more effective agents for monotherapy, combination drug therapy tailored to the individual patient may offer lasting clinical benefit.

PRINCIPLES FOR TREATING COMPLICATED PATIENTS WITH COMPLEX DRUG REGIMENS

The following principles are intended to apply to a patient who is refractory to monotherapy with one or more standard agents, in spite of good tolerability:

- Treat actively to remission early in the disease.
- Maintain regimens that are effective, unless side effects are problematic.
- Select initial agents based on good tolerability, to increase compliance.
- Increase the dosage slowly to maximal efficacy with appearance of minimal side effects.
- Continue monotherapy, adding a second drug with a different mechanism of action.
- Carefully select a second drug with a thorough understanding of its pharmacology, to help manage comorbid symptoms and reduce undesirable side effects, if any, of the first agent (eg, using lithium with carbamazepine to maintain WBC counts).
- For patients who respond only partially, add or remove a drug only for reasons of inefficacy or excessive side effects. In patients who are not very ill, one may consider reducing the dosage of the first agent. In very sick patients, however, this may cause relapse.
- For women of reproductive age, start with a drug safe for pregnancy. Alternatively, one may switch to such a drug 6 months prior to a planned pregnancy, and switch back after childbirth. Calcium antagonists are a good alternative to lithium or anticonvulsants in the first trimester.

References

1. Regier DA, Boyd JH, Rae DS, et al. One-month prevalence of mental disorders in the United States: Based on five epidemiologic catchment area sites. *Arch Gen Psychiatry.* 1988;45:977-986.
2. Weissman MMJ, Leaf PJ, Tischer GL, et al. Affective disorders in five United States communities. *Psychol Med.* 1988;18:141-153.
3. Robins LN, Regier DA, eds. *Psychiatric Disorders in America: the Epidemiologic Catchment Area* Study. New York, NY: Free Press; 1991.
4. Kessler RC, McGonagle KA, Zhao S, et al. Lifetime and 12-month prevalence of DSM-III-R psychiatric disorders in the United States: results from the National Co-Morbidity Survey. *Arch Gen Psychiatry.* 1994;51:8-19.
5. Weissman MM, Bland RC, Canino GJ, et al. Cross-national epidemiology of major depression and bipolar disorder. *JAMA.* 1996;276:293-299.
6. Angst J. Epidemiology of the bipolar spectrum. *Encephale.* 1995;21:37-42.
7. Hilty DM, Brady KT, Hales RE. A review of bipolar disorder among adults. *Psychiatr Serv.* 1999;50:201-213.
8. Tsuang MT, Woolson RF. Excess mortality in schizophrenia and affective disorders. Do suicides and accidental deaths solely account for this excess? *Arch Gen Psychiatry* 1978;35:1181-1185.
9. Akiskal HS, Maser JD, Zeller PJ, et al. Switching from 'unipolar' to bipolar II. *Arch Gen Psychiatry.* 1995;52:114-123.
10. Goodwin FK, Jamison KR. *Manic-Depressive Illness.* New York, NY: Oxford University Press; 1990.
11. McElroy SL, Keck PE Jr., Pope HG, et al. Clinical and research implications of the diagnosis of dysphoric or mixed mania or hypomania. *Am J Psychiatry.* 1992;149:1633-1644.
12. Paterson AD, Naimark DMJ, Vincent JB, et al. Genetic anticipation in neurological and other disorders. In: Wells RD, Warren ST, eds. *Genetic Instabilities and Hereditary Neurological Diseases.* San Diego, Calif: Academic Press; 1998.
13. Macedo A, Azevedo H, Coelho I, et al. Genetic anticipation in Portuguese families with bipolar mood disorders. *CNS Spectrums.* 1999;4:25-31.
14. McInnis MG, McMahon FJ, Chase GA, et al. Anticipation in bipolar disorder. *Am J Hum Genet.* 1993;53:385-390.
15. Greenberg PE, Stiglin LE, Finkelstein SN, et al. The economic burden of depression in 1990. *J Clin Psychiatry.* 1993;54:405-418.
16. Keck PE, Bennett JA, Stanton SP. Health-economic aspects of the treatment of manic-depressive illness with divalproex. *Rev Contemp Pharmacotherapy.* 1995;6:597-604.
17. National survey of NDMDA members finds long delay in diagnosis of manic-depresssive illness. *Hosp Community Psychiatry.* 1993;44:800-802.
18. Calabrese JR, Woyshville MJ. A medication algorithm for treatment of bipolar rapid cycling? *J Clin Psychiatr.* 1995;56(suppl 3):11-18.
19. Tondo L, Baldessarini RJ. Rapid cycling in women and men with bipolar manic-depressive disorders. *Am J Psychiatry.* 1998;155:1434-1436.
20. Angst J. The course of affective disorders. II. Typology of bipolar manic-depressive illness. *Arch Psychiatr Nervekr.* 1978;226:65-73.
21. Roy-Byrne P, Post RM, Uhde TW et al. The longitudinal course of recurrent affective illness: life chart data from research patients at the NIMH. *Acta Psychiatr Scand.* (suppl)1985;317:1-34.
22. McElroy SL, Strakowski SM, Keck PE Jr. et al. Differences and similarities in mixed and pure mania. *Compr Psychiatry.* 1995;36:187-194.
23. Matsunaga H, Sarai M. Elevated serum LH and androgens in affective disorder related to the menstrual cycle: with reference to polycystic ovary syndrome. *Jpn J Psychiatry Neurol.* 1993;47:825-842.
24. Kendell RE, Chalmers JC, Platz C. Epidemiology of puerperal psychoses [published erratum appears in Br J Psychiatry. 1987;151:135] *Br J Psychiatry.* 1987;150:662-673.
25. Dean C, Williams RJ, Brockington IF. Is puerperal psychosis the same as bipolar manic-depressive disorder? A family study. *Psychol Med.* 1989;19:637-647.
26. Althshuler LL, Cohen LS, Szuba MP, et al. Pharmacologic management of psychiatric illness during pregnancy: dilemmas and guidelines. *Am J Psychiatry.* 1996;153:592-606.
27. Stowe ZN, Nemeroff CB. Psychopharmacology during pregnancy and lactation. In: Schaatzberg AF, Nemeroff CB, eds. *Textbook of Psychopharmacology.* Washington, DC; American Psychiatric Press. 1995:823-835.
28. Cohen LS, Sichel DA, Robertson LM, Hecksher E, et al. Post-partum prophylaxis for women with bipolar disorder. *Am J Psychiatry.* 1995;152:1641-1644.
29. Maj M, Maliano L, Pirozzi R, Marasco C, Guarneri M. Validity of rapid cycling as a course specifier for bipolar disorder. *Am J Psychiatry.* 1994;15:1015-1019.
30. Bowden CL, Calabrese JR, McElroy SL, et al. The efficacy of lamotrigine in rapid cycling and non-rapid cycling patients with bipolar disorder. *Biol Psychiatry.* 1999;45:953-958.
31. Calabrese JR, Bowden CL, Sachs GS, et al. A double-blind placebo-controlled study of lamotrigine monotherapy in outpatients with bipolar I depression. Lamictal 602 Study Group. *J Clin Psychiatry.* 1999;60:79-88.
32. Frye MA, Ketter Ta, Osuch EA et al. Gabapentin and lamotrigine monotherapy in mood disorder: an Update, Syllabus and Proceedings Summary, APA Annual Meeting, May 30-June 4, 1998, Toronto Canada. No. 77D, 150.
33. Pies R. Somatic treatment advances for bipolar disorder: a review. *Psych Times.* 1997;14:56-60.
34. Keitner GI, Ryan CE, Miller IW, et al. 12-month outcome of patients with major depression and comorbid psychiatric or medical illness (compound depression). *Am J Psychiatry.* 1991;148:345-350.
35. Regier DA, Farmer ME, Rae DS, et al. Comorbidity of mental disorders with alcohol and other drug abuse: results from the ECA study. *JAMA.* 1990;204:2511-2518.
36. Kessler RC, Nelson CB, McGonagle KA, et al. The epidemiology of co-occurring addictive and mental disorders: implications for prevention and service utilization. *Am J Orthopsychiatry.* 1996;66:17-31.
37. Brady KT, Sonne SC, Anton R, et al. Valproate in the treatment of acute bipolar affective episodes complicated by substance abuse: a pilot study. *J Clin Psychiatry.* 1995;56:118-121.
38. Keck PE Jr, McElroy SL, Friedman LM. Valproate and carbamazepine in the treatment of panic and posttraumatic stress disorders, withdrawal states, and behavioral dyscontrol syndromes. *J Clin Psychopharmacol.* 1992;12(suppl 1):36-41.
39. Maj M, Pirozzi R, Magliano L. Nonresponse to reinstituted lihtium prophylaxis in previously responsive bipolar patients: prevalence and predictors. *Am J Psychiatry.* 1995;152:1810-1811.
40. Boyd JH, Burke JD Jr, Gruenberg E et al. Exclusion criteria of DSM-III: a study of co-occurrence of hierarchy-free syndromes. *Arch Gen Psychiatry.* 1984;41:983-989.
41. Jefferson JW, Greist JH, Perse TL et al. Fluvoxamine-associated mania/hypomania in patients with obsessive-compulsive disorder (letter). *J Clin Psychopharmacol.* 1991;11:391-392.
42. Winokur G, Coryell W, Endicott J. Further distinctions between manic-depressive illness (bipolar disorder and primary depressive disorder (unipolar depression). *Am J Psychiatry.* 1993;150: 1176-1181.
43. Pary RJ, Levitas AS, DesNoyers Hurley A. Diagnosis of bipolar disorder in persons with developmental diabilities. *Ment Health Asp Dev Disabil.* 1999;2:37-49.
44. Lowry MA. Unmasking mood disorders: recognizing and measuring symptomatic behaviors. The *Habilitative Mental Healthcare Newsletter* 1997;16:1-6.
45. Keller MB, Lavori PW, Coryell W. Bipolar I: a five year prospective follow-up. *J Nerv Ment Dis.* 1993;181:238-245.
46. Tohen M, Waternaux CS, Tsuang MT. Outcome in mania: a 4-year prospective follow-up of 75 patients utilizing survival analysis. *Arch Gen Psychiatry.* 1990;47:1106-1111.
47. Keller MB, Waternaux CM, Tsuant MT. Bipolar I: a five-year prospective follow-up. *J Nerv Mental Dis.* 1993;181:238-245.
48. Suppes T, Baldessarini RJ, Faedda GL, et al. Risk of recurrence following discontinuation of lithium treatment in bipolar disorder. *Arch Gen Psychiatry.* 1991;48:1082-1088.
49. Solomon DA, Keitner GI, Miller IW, et al. Course of illness and maintenance treatment for patients with bipolar disorder. *J Clin Psychiatry.* 1995;56:5-13.
50. Keck PE Jr, McElroy SL. Outcome in the pharmacologic treatment of bipolar disorder. *J Clin Psychopharmacol.* 1996;16(suppl 1):15-23.
51. Griel W, Ludwig-Mayerhofer W, Erazo N et al. Lithium versus carbamazepine in the maintenance treatment of bipolar disorders: a randomized study. *J Affec Disord.* 1997;43:151-161.
52. Data on file, Abbott Laboratories.
53. Young RC, Klerman C. Mania in late life: focus on age at onset. *Am J Psychiatry.* 1992;149:867-876.
54. Dunner DL, Fieve RR. Clinical factors in lithium carbonate prophylaxis failure. *Arch Gen Psychiatry.* 1974;30:229-233.
55. Coryell W, Endicott J, Keller M. Rapidly cycling affective disorder. *Arch Gen Psychiatry.* 1992;49:126-131.
56. Bowden CL. Predictors of response to divalproex and lithium. *J Clin Psychiatry.* 1995;56 (suppl 3):25-30.
57. Kramlinger KG, Post RM. Ultra-rapid and ultradian cycling in bipolar affective illness. *Br J Psychiatry.* 1996;168:314-323.
58. Pazzaglia PJ, Post RM, Ketter TA, George MS, et al. Preliminary controlled trial of nimodipine in ultra-rapid cycling affective dysregulation. *Psychiatry Res.* 1993;49:257-272.
59. Pazzaglia PJ, Post RM, Ketter TA, et al. Nimodipine monotherapy and carbamazepine augmentation in patients with refractory recurrent affective illness. *J Clin Psychopharmacol.* 1998;18:404-413.
60. Calabrese JR, Markovitz PJ, Kimmel SE, et al. Spectrum of efficacy of valproate in 78 rapid-cycling bipolar patients. *J Clin Psychopharmacol.* 1992;12(suppl 1):53-56.
61. Bauer MS, Whybrow PC. Rapid cycling bipolar affective disorder. *Arch Gen Psychiatr.* 1990;47:435-440.
62. Hirschfeld RMA, Clayton PJ, Cohen I, et al. Practice Guidelines for the Treatment of Patients With Bipolar Disorder. *Am J Psychiatry.* 1994;151(suppl 12):1-36.
63. Frances A, Doherty JP, Kahn DA. Treatment of bipolar disorder. *J Clin Psychiatry.* 1996;57(suppl 12A):1-8.
64. Sachs Gs, Lafer B, Stoll AL. A double-blind trial of bupropion versus desipramine for bipolar depression. *J Clin Psychiatry.* 1994;55:391-393.
65. Zornberg GL, Pope HG. Treatment of depression in bipolar disorder: new directions for research. *J Clin Psychopharmacol.* 1993;13:397-408.
66. Sachs GS. Treatment-resistant bipolar depression. *Psychiatr Clin North Am.* 1996;19:215-236.
67. Goldberg JF, Harrow M, Grossman LS. Course and outcome in bipolar affective disorder: a longitudinal follow-up study. *Am J Psychiatry.* 1995;152:379-384.
68. Tsuang MTA, Woolson RF, Fleming M. Long-term outcome of major psychosis I. Schizophrenia and affective disorders compared with psychiatrically symptom-free surgical conditions. *Arch Gen Psychiatry.* 1979 Nov;36(12)1295-301
69. Janicak PG, Davis JM, Preskorn SH, et al. *Principles and Practice of Psychopharmacology.* Baltimore, Williams & Wilkins, 1993.
70. Grof P, Alda M, Grof E, Fox D, et al. The challenge of predicting response to stabilizing lithium treatment: the importance of patient selection. *Br J Psychiatry.* 1993;163:16-19.
71. Faedda GL, Baldessarini RJ, Tohe M, et al. Episode sequence in bipolar disorder and response to lithium treatment. *Am J Psychiatry.* 1991;148:1237-1239.
72. Calabrese JR, Fatemi SH, Kujawa M, et al. Predictors of response to mood stabilizers. *J Clin Psychopharmacol.* 1996;16(2 suppl 1):24S-30S.
73. Denicoff KD, Smith-Jackson EE, Disney ER, et al. Comparative efficacy of lithium, carbamazepine, and the combination in bipolar disorder. *J Clin Psychiatry.* 1997;58:470-478.
74. Gelenberg AJ, Kane JN, Keller MB. Comparison of standard and low serum levels of lithium for maintenance treatment of bipolar disorders. *N Engl J Med.* 1989;321:1489-1493.
75. Koukopoulos A, Reginaldi D, Minnai G, et al. The long term prophylaxis of affective disorders. *Adv Biochem Psychopharmacol.* 1995;49:127-147.
76. Markar HR, Mander AJ. Efficacy of lithium prophylaxis in clinical practice. *Br J Psychiatry.* 1989;15:496-500.
77. Vestergaard P. Treatment and prevention of mania: a Scandinavian perspective. *Neuropsychopharmacol.* 1992;7:249-260.
78. Faedda GL, Tondo L, Baldessarini RJ, et al. Outcome after rapid versus gradual discontinuation of lithium treatment in bipolar disorders. *Arch Gen Psychiatry.* 1993;50:448-455.
79. Goodwin FK. Anticonvulsant therapy and suicide risk in affective disorders. *J Clin Psychiatry.* 1999;60(suppl):89-93.
80. Nonaka S, Katsube N, Chuang DM. Lithium protects rat cerebellar granule cells against apoptosis induced by anticonvulsants, phenytoin and carbamazepine. *J Pharmacol Exp Ther.* 1998;286: 539-547.
81. Amdisen A. Serum lithium levels and clinical pharmacokinetics of lithium. *Clin Pharmacokinet.* 1977;2:73-92.
82. Goodnick PJ, Fieve RR, Meltzer HL, et al. Lithium elimination half-life and duration of therapy. *Clin Pharmacol Ther.* 1981;29:47-50.

83. Schou M, Juel-Nielsen N, Stromgren E et al. The treatment o manic psychoses by the administration of lithium salts. *J Neurol Neurosurg Psychiatry.* 1954;17:250-260.
84. Maggs R. Treatment of manic illness with lithium carbonate. *Br J Psychiatry.* 1963;109:56-65.
85. Koukopoulos A, Reginaldi D, Johnson FN. Fluctuations in serum lithium levels as a function of mood state. *Lithium.* 1992;3:195-201.
86. Gitlin MJ, Jamison KR. Lithium clinics: theory and practice. *Hosp Comm Psychiatry.* 1984;35:363-368.
87. Cohen LS. The use of psychotropic drugs during pregnancy and puerperium. *Curr Affect Illness.* 1992;11:5-13.
88. Nora JJ, Nora AH, Toews WH. Lithium, Ebstein's anomaly and other congenital heart defects. *Lancet.* 1974;2:594-595.
89. Cohen LS, Friedman JM, Jefferson JW et al. A reevaluation of risk of in utero exposure to lithium. [published erratum appears in *JAMA* 1994;271:1485] *JAMA.* 271:146-150.
90. Bowden CL, Brugger AM, Swann AC, Calabrese JR et al. Efficacy of divalproex vs. lithium and placebo in the treatment of mania. *JAMA.* 1994;271:918-924.
91. McElroy SL, Keck PE Jr, Pope HG Jr. Sodium valproate: its use in primary psychiatric disorders. *J Clin Psychopharmacol.* 1987;7:16-24.
92. Bowden CL, Janicak PG, Orsulak P, et al. Relation of serum valproate concentration to response in mania. *Am J Psychiatry.* 1996;153:765-770.
93. Hurst DL. Expanded therapeutic range of valproate. *Pediatr Neurol.* 1987;3:342-344.
94. Ohtsuka Y, Amano R, Mizukawa M, et al. Treatment of intractable childhood epilepsy with high-dose valproate. *Epilepsia.* 1992;33:158-164.
95. Keck PE, McElroy SL, Tugrul KC, et al. Valproate oral losding in the treatment of acute mania. *J Clin Psychiatry.* 1993;54:305-308.
96. May RB, Sunder TR. Hematological manifestations of long-term valproate therapy. *Epilepsia.* 1993;34:1098-1101.
97. Lindout D, Schmidt D. In utero exposure to valproate and neural tube defects. *Lancet.* 1986;1392-1393.
98. McElroy SL, Keck PK. Antiepileptic drugs. In: Schaatzberg AF, Nemeroff CB eds. *Textbook of Psychopharmacology.* Washington, DC; American Psychiatric Press. 1995:351-375.
99. Post RM. Alternatives to lithium for bipolar affective illness. In: Tasmana, ed. *Review of Psychiatry.* Washington, DC; American Psychiatric Press. 1990:170-202.
100. Okuma T. Effects of carbamazepine and lithium on affective disorders. *Neuropsychobiology.* 1993;27:138-145.
101. Ketter TA, Kimbrell Ta, George MS, et al. Baseline cerebral hypermetabolism associated with carbamazepine response, and hypometabolism with nimodipine response in mood disorders. *Biol Psychiatry.* 1999;46:1364-1374.
102. Ketter TA, Flockhart DA, Post RM, et al. The emerging role of cytochrome P450 3A in psychopharmacology. *J Clin Psychopharmacol.* 1995;15:387-398.
103. Denicoff KD, Smith-Jackson E, Disney E et al. Outcome in bipolar patients randomized to lithium or carbamazepine prophylaxis and crossed over in year two. First International Conference on Bipolar Disorder [abstract] Pittsburgh, Pa; 1994.
104. Rosa FW. Spina bifida in infants of women treated with carbamazepine during pregnancy. *N Engl J Med.* 1991;324:674-677.
105. Mukherjee S, Sackheim HA, Schnurr DB. ECT of acute manic episodes: a review. *Am J Psychiatry.* 1994;151:169-176.
106. Mukherjee S, Sackeim HA, Lee C. Unilateral ECT in the treatment of manic episodes. *Convulsive Therapy.* 1988;4:74-80.
107. Black DW, Winokir G, Nasrallah H. Treatment of mania: a naturalistic study of ECT vs. lithium in 438 patients. *J Clin Psychiatry.* 1987;48:132-139.
108. McCabe MS, Norris B. ECT vs. chlorpromazine in mania. *Biol Psychiatry.* 1977;12:245-254.
109. Denicoff KD, Smith-Jackson EE, Bryan AL, et al. Valproate prophylaxis in a prospective clinical trial of refractory bipolar disorder. *Am J Psychiatry.* 1997;154:1456-1458.
110. Lerer B, Moore N, Meyendorff E et al. Carbamazepine vs. lithium in mania: a double-blind study. *J Clin Psychiatry.* 1987;48:89-93.
111. Okuma T, Yamashita I, Takahashi R, et al. Comparison of the antimanic efficacy of carbamazepine and lithium carbonate by double-blind controlled study. *Pharmacopsychiatry.* 1990;23:143-150.
112. Small JG, Klapper MH, Milstein V et al. Carbamazepine compared with lithium in the treatment of mania. *Arch Gen Psychiatry.* 1991;48:915-921.
113. Amiloride in the treatment of lithium-induced diabetes insipidus [letter]. *N Engl J Med.* Anon. 1985;312:1575-1577.
114. Calabrese JR, Fatemi SH, Woyshville MJ et al. Lamotrigine in rapid cycling bipolar disorder. *Amer J Psychiatry.* 1996;153:1236.
115. Kusumakar V, Yatham LN. An open study of lamotrigine in refractory bipolar depression. Brief report submitted for publication.
116. Yatham LN, Kusumakar V. Lamotrigine in bipolar depression. *Am J Psychiatr.* [Letter, in press].
117. Yatham LN, Kusumakar V. Treatment of bipolar depression In: Conference on Mood disorders: Recent Advances. Halifax, Canada, Oct 1996.
118. Frye MA et al. *J Clin Psychopharmacol.* [In press].
119. Calabrese JR, Rapport DJ, Shelton MD, et al. Clinical studies on the use of lamotrigine in bipolar disorder. *Neuropsychobiol.* 1998;38:185-191.
120. Calabrese JR, Bowden CL, Rhodes LJ et al. Lamotrigine in treatment-refractory bipolar disorder. Presented at the annual meeting of the American Psychiatric Association, New York: May 4-9, 1996.
121. Sporn J, Sachs G. The anticonvulsant lamotrigine in treatment-refractory manic-depressive illness. *J Clin Psychopharmacology.* 1997;17:185-189.
122. Young LT, Rob JC, Patelis-Siotis I, et al. Acute treatment of bipolar depression with gabapentin. *Biol Psychiatry.* 1997;42:851-853.
123. Schaffer CB, Schiffer LC. Gabapentin in the treatment of bipolar disorder. *Am J Psychiatry.* 1997;154:291-292.
124. Dunayevich E, Sax KW, Keck PE Jr, et al. Twelve-month outcome in bipolar patients with and without personality disorders. *J Clin Psychiatry.* 2000;61:134-139.
125. Grunze H, Erfurth A, Marcuse A, et al. Tiagabine appears not to be efficacious in the treatment of acute mania. *J Clin Psychiatry.* 1999;60:759-762.
126. Joffe RT, Singer W, Levitt AJ, et al. A placebo-controlled comparison of lithium and triiodothyronine augmentation of tricyclic antidepressants in unipolar refractory depression. *Arch Gen Psychiatry.* 1993;50:387-393.
127. Cooke RG, Joffe RT, Levitt AJ. T3 augmentation of antidepressant treatment in T4-replaced thyroid patients. *J Clin Psychiatry.* 1992;53:16-18.
128. Stancer HC, Persad E. Treatment of intractable rapid-cycling manic-depressive disorder with levothryoxine. *Arch Gen Psychiatry.* 1982;39:311-312.
129. Whybrow PC. The therapeutic use of triiodothyronine and high dose thyroxine in psychiatric disorder. *Acta Med Austriaca.* 1994;21:47-52.
130. Baumgartner A, Bauer M, Hellweg R. Treatment of intractable non-rapid cycling bipolar affective disorder with high-dose thyroxine, an open clinical trial. *Neuropsychopharmacol.* 1994;10:183-189.
131. Whybrow PC, personal communication.
132. Frye MA, Denicoff KD, Luckenbaugh DA, et al. Thyroid potentiation in affective illness. *APA New Research Program and Abstracts,* 1997: abstract NR425.
133. Center J, Beange H, McElduff A. People with mental retardation have an increased prevalence of osteoporosis: a population study. *Am J Mental Retardation.* 1998;103:19-28.
134. Post RM, Kimbrell TA, McCann UD, et al. Repetitive transcranial magnetic stimulation as a neuropsychiatric tool: present status and future potential. *J ECT.* 1999;15:39-59.
135. Kimbrell TA, Little JT, Dunn RT, et al. Frequency dependence of antidepressant response to left prefrontal repetitive transcranial magnetic stimulation (rTMS) as a function of baseline cerebral glucose metabolism. *Biol Psychiatry.* 1999;46:1603-1613.
136. Bradwejn J, Shriqui C, Kosycki D et al. Double-blind comparison of the effects of clonazepam and lorazepam in acute mania. *J Clin Psychopharmacol.* 1990;10:403-408.
137. Sernyak MJ, Woods SW. Chronic neuyroleptic use in manic-depressive illness. *Psychopharmacologic Bull.* 1993;29:375-381.
138. McElroy SL, Beck PE, Strakowski SM. Mania, psychosis and antipsychotics. *J Clin Psychiatry.* 1996;57(suppl 3):14-26.
139. Tohen M, Sanger TM, McElroy SL, et al. Olanzapine versus placebo in the treatment of acute mania. Olanzapine HGEG Study Group. *Am J Psychiatry.* 1999;156:702-709.
140. Manna V. Bipolar affective disorders and the role of intraneuronal calcium. Therapeutic effects of the treatment with lithium salts and/or calcium antagonist in patients with rapid polar inversion. *Minerva Med.* 1991;82:757-763.
141. Banov MD, Zarate CA Jr, Tohen M, et al. Clozapine therapy in refractory affective disorders: polarity predicts response in long-term follow-up. *J Clin Psychiatry.* 1994;55:295-300.
142. Calabrese JR, Kimmel SE, Woyshville MJ et al. Clozapine for treatment refractory mania. *Am J Psychiatry.* 1996;153:759-764.
143. Ghaemi SN, Sachs GS. Long-term risperidone treatment in bipolar disorder: 6-month follow up. *Int Clin Psychopharmacol.* 1997;12:333-338.
144. Ghaemi SN, Katzow JJ. The use of quetiapine for treatment-resistant bipolar disorder: a case series. *Ann Clin Psychiatry.* 1999;11:137-140.
145. Altshuler LL, Post RM, Leverich GS et al. Antidepressant-induced mania and cycle acceleration: a controversy revisited. *Am J Psychiatry.* 1995;152:1130-1138.
146. Wehr TA, Goodwin FK. Rapid cycling in manic-depressives induced by tricyclic antidepresants. *Arch Gen Psychiatry.* 1979;36:555-559.
147. Srisuraponant M, Yatham LN, Zis AP. Treatment of acute bipolar depression: a review of literature. *Can J Psychiatry.* 1995;40:533-544.
148. Dubovsky SL. Calcium antagonists in manic-depressive illness. *Neuropsychobiology.* 1993;27:184-192.
149. Walden J, Fritze J, Van Calker D, et al. A calcium antagonist for the treatment of depressive episodes: single case reports. *J Psychiat Res.* 1995;29:71-76.
150. Walden J, Grunze H, Mayer A, et al. Calcium antagonist effects of carbamazepine in epilepsies and affective psychoses. *Neuropsychobiology.* 1993;27:171-175.
151. Baldessarini RJ. Drugs and the treatment of psychiatric disorders: depression and mania. In: Hardman JG, Limbird LE, et al (eds) Goodman & Gilman's *The Pharmacological Basis of Therapeutics.* 9th ed. New York: Raven Press. 1995:431-459.
152. Post RM, Ketter TA, Denicoff K, et al. The place of anticonvulsant therapy in bipolar illness. *Psychopharmacology.* 1996;128:115-129.
153. Bennett J, Goldman WT, Suppes T. Gabapentin for treatment of bipolar and schizoaffective disorders. *J Clin Psychopharmacol.* 1997;17:141-142.
154. Walden J, Grunze H, Bingmann D, et al. Calcium antagonistic effects of carbamazepine as a mechanism of action in neuropsychiatric disorders: studies in calcium dependent model epilepsies. *Eur Neuropsychopharmacol.* 1992;2:455-462.
155. Robertson RM, Robertson D. Drugs used for the treatment of myocardial ischemia. In: Hardman JG, Limbird LE et al, eds. Goodman & Gilman's *The Pharmacological Basis of Therapeutics.* 9th ed. New York, NY: Raven Press. 1995:759-779.
156. Calcium channel blocking drugs. In: *AMA Drug Evaluations.* Summer, 1994:581-599.
157. Dubovsky SL, Buzan RD. Novel alternatives and supplements to lithium and the anticonvulsants for bipolar affective disorder. *J Clin Psychiatry.* 1997;58:224-242.
158. Caillard V, Masse G. Treatment of mania by a calcium inhibitor. Preliminary study. *Encephale.* 1982;8:587-594.
159. Dubovsky SL. Calcium channel antagonists as novel agents for manic-depressive disorder. In: Schatzberg AF, Nemeroff CB, eds. *Textbook of Psychopharmacology.* American Psychiatric Press, Washington, DC, 1995;377-388.
160. Pazzaglia PJ, George MS, Post RM, et al. Nimodipine increases CSF somatostatin in affectively ill patients. *Neuropsychopharmacol.* 1995;13:75-83.
161. Goodnick PJ. Nimodipine treatment of rapid cycling bipolar disorder. *J Clin Psychiatr.* 1995;56:330.
162. Brunet G, Cerlich B, Robert P, et al. Open trial of a calcium antagonist, nimodipine, in acute mania. *Clin Neuropharmacol.* 1990;13:224-228.
163. Grunze H, Walden J, Wolf R, et al. Combined treatment with lithium and nimodipine in a bipolar I manic syndrome. *Prog Neuro-Psychopharmacol & Biol Psychiatry.* 1996;20:419-426.
164. Hesslinger B, Riedel H, Hellwig B, et al. Phase prevention in bipolar affective disorder with nimodipine. A case report (German). *Nervenarzt.* 1996;67:394-396.
165. Davanzo PA, Krah N, Kleiner J, et al. Nimodipine treatment of an adolescent with ultradian cycling bipolar affective disorder. *J Child Adolesc Psychopharmacol.* 1999;9:51-61.
166. Zabihian J, Benefield WH. Drug information update. *Habilitative Mental Healthcare Newsletter.* 1996;15:97-100.

POST-TEST

BIPOLAR DISORDER: an overview of current treatment with a focus on the role of calcium channel blockers

To obtain a certificate of completion for 2 hours of category 1 credit toward the AMA Physician's Recognition Award, you must complete the exam by selecting the best answer to each question, complete the evaluation form and mail to the Postgraduate Institute for Medicine. At least 15 of the 20 answers must be correct to obtain a certificate of completion.

1. Which of the following statements is not true?

a. The mean age of onset for bipolar I and II disorders is 21 years.

b. Bipolar disorder is undiagnosed or misdiagnosed for an average of 8 years after the initial episode.

c. Bipolar illness of late onset is more commonly associated with rapid cycling, mixed states, substance abuse, and psychotic features.

d. Bipolar illness of early onset is more likely to respond to treatment with drugs other than lithium.

---

2. The theoretical savings in the first year of efficient treatment of bipolar disorder would be

a. $10.5 million
c. $500 million
b. $100 million
d. $1.5 billion

---

3. Comorbid states

a. are a predictor of poorer outcome and treatment response.

b. include OCD, which is 18 times more likely to occur in patients with bipolar disorder than in the general population.

c. include ADHD, which is difficult to diagnose because the symptoms of ADHD may also be features of a manic or hypomanic episode.

d. All of the above are correct.

---

4. The estimated rates of relapse and recurrence after the initial episode are

a. 10%-20%
c. 60%-70%
b. 40%-50%
d. 80%-90%

---

5. Bipolar disorder can present as

a. mixed states.

b. rapid cycling.

c. manic, hypomanic, and depressive episodes.

d. All of the above are correct.

6. Antidepressant mediations may be safely prescribed for bipolar depression without risk of inducing a manic state.

a. True
b. False

---

7. Five of 6 studies suggested that bipolar and unipolar depression respond equally well to

a. lithium.
c. ECT.
b. valproate.
d. none of the above.

---

8. The US Food and Drug Administration has given approval to ___ for treatment of bipolar illness.

1) lithium
3) carbamazepine
2) valproate
4) phenytoin

a. 1
c. 1, 2, and 3
b. 1 and 2
d. 1, 2, 3, and 4

---

9. In general, predictors of a poor response to lithium include

1) depression followed by mania.

2) multiple previous episodes.

3) rapid cycling.

4) excellent interepisode recovery.

5) personality disorder.

a. 1, 2, and 4
c. all of the above
b. 1, 2, 3, and 5
d. none of the above

---

10. Many clinicians prefer valproate to lithium because

a. valproate has a shorter time to onset of action.

b. valproate has a larger serum therapeutic range which is associated with lack of need for blood level monitoring.

c. valproate has apparent efficacy in maintenance treatment.

d. All of the above are correct.

Post-test continues on following page

Post-test continued

11. Which of the following statements about carbamazepine is/are true?

1) It is effective for the treatment of acute mania, mixed state, or secondary bipolar disorder.
2) It has a large therapeutic index.
3) It induces its own hepatic metabolism, as well as that of many other drugs.
4) Neural tube defects have been reported when carbamazepine was used in the first trimester of pregnancy.

a. 1, 2, and 3 **c.** all of the above
b. 1, 3, and 4 **d.** none of the above

---

12. For many clinicians, elevations in liver enzymes of up to 3 to 4 times normal are not necessarily cause for concern, particularly if albumin, protein, and clotting factors are unaffected, indicating adequate liver function.

a. True **b.** False

---

13. Which of the following statements about lamotrigine is not true?

a. Lamotrigine has shown promise in bipolar depression and rapid cycling in open studies.
b. When lamotrigine is used in combination with valproate, one half the recommended dose should be used.
c. When lamotrigine is used in combination with carbamazepine, one half the recommended dose should be used.
d. Lamotrigine causes a macular, papular, puritic rash in about 5% to 10% of patients.

---

14. The US Food and Drug Administration has recently approved ___ for the treatment of acute mania.

a. olanzapine **c.** quetiapine
b. risperidone **d.** lorazepam

---

15. Observations of the association of bipolar depression and mania with elevated intracellular calcium ion signaling have led to investigation of the use of calcium channel blockers in bipolar disorder.

a. True **b.** False

16. Which of the following calcium channel blockers has/have been studied in bipolar disorder?

a. Verapamil, diltiazem, nimodipine
b. Amlodipine and isradipine
c. Nifedipine and felodipine
d. All of the above are correct.

---

17. The lipophilicity of a calcium channel blocker is a consideration when devising a therapeutic strategy because high lipophilicity permits penetration of the blood-brain barrier and enables activity at doses that have little or no effects on blood pressure and heart rate.

a. True **b.** False

---

18. Dihydropyridine type calcium channel blockers

1) may be effective as antimanic agents
2) have a greater degree of peripheral vasodilation, accompanied by a sufficient increase in sympathetic tone to overcome the negative inotropic effect.
3) possess antiarrhythmic properties.
4) all have strongly active metabolites.

a. 1 and 2 **c.** 1, 2, and 3
b. 2 and 3 **d.** All of the above are correct.

---

19. Combination drug therapy can be more useful than monotherapy because

a. use of a new drug may be highly effective especially when dose escalation is not effective or tolerable.
b. it may be possible to use lower doses, with less toxicity resulting, and a more persistent therapeutic effect.
c. fewer side effects may increase compliance
d. combination therapy tailored to the individual patient may offer lasting clinical benefit.
e. All of the above are correct.

---

20. Which of the following statements apply to treating a patient who is refractory to monotherapy with one or more standard agents?

a. Maintain regimens that are effective, unless side effects are problematic.
b. Continue the monotherapy agent, adding a second drug with a different mechanism of action.
c. For women of reproductive age, start with a drug safe for pregnancy.
d. All of the above are correct.

EVALUATION FORM: BIPOLAR DISORDER: an overview of current treatment with a focus on the role of calcium channel blockers

A certificate of completion is issued only upon receipt of your completed evaluation form and exam for credit (15 out of 20 quiz answers must be correct).

Please answer the following questions by circling the appropriate rating:
5 = Outstanding 4 = Good 3 = Satisfactory 2 = Fair 1 = Poor

Extent to Which Program Activities Met the Identified Objectives

Upon completion of this activity, participants should be able to:

- Describe the standard treatment modalities that are commonly used in the treatment of bipolar disorder — 5 4 3 2 1
- Describe examples of treatment with various medications in off-label use that can be therapeutic in individuals with resistant illness — 5 4 3 2 1
- Explain the role of calcium channel blockers in the treatment of resistant cases of bipolar disorder — 5 4 3 2 1
- Give examples of treatment regiments using calcium channel blockers that may be useful in resistant cases of bipolar disorder. — 5 4 3 2 1

Overall Effectiveness of the Activity

Related to my practice needs	5 4 3 2 1
Will influence how I practice	5 4 3 2 1
Will help me improve patient care	5 4 3 2 1
Stimulated my intellectual curiosity	5 4 3 2 1
Overall quality of material	5 4 3 2 1
Overall, the activity met my expectations	5 4 3 2 1
Avoided commercial bias or influence	5 4 3 2 1

Will the information presented cause you to make any changes in your practice? ☐ Yes ☐ No

How committed are you to making these changes?
5 (very committed) 4 3 2 1 (not at all committed)

If yes, please describe any change(s) you plan to make in your practice as result of this activity.

Please list any other topics that would be of interest to you for future educational activities:

Degree: ☐ MD ☐ DO ☐ PA Other_____

To obtain a certificate of completion for 2 hours of category 1 credit toward the AMA Physician's Recognition Award, you must complete the exam by selecting the best answer to each question, complete the evaluation form and mail to the Postgraduate Institute for Medicine. At least 15 of the 20 answers must be correct to obtain a certificate of completion.

If you wish to receive credit for this activity, please fill in your name and address and mail or fax to: Postgraduate Institute for Medicine, P.O. Box 260620, Littleton, CO 80163-0620 (FAX) 303-790-4876.

1.	A	B	C	D	11.	A	B	C	D
2.	A	B	C	D	12.	A	B		
3.	A	B	C	D	13.	A	B	C	D
4.	A	B	C	D	14.	A	B	C	D
5.	A	B	C	D	15.	A	B		
6.	A	B			16.	A	B	C	D
7.	A	B	C	D	17.	A	B	C	D
8.	A	B	C	D	18.	A	B	C	D
9.	A	B	C	D	19.	A	B	C	D
10.	A	B	C	D	20.	A	B	C	D

NAME_____

_____

SPECIALTY _____

STREET ADDRESS _____ BOX/SUITE _____

CITY _____ STATE _____ ZIP CODE _____

PHONE ( ) _____ FAX ( ) _____

SIGNATURE _____

I certify my actual time spent to complete this educational activity to be _____ hour(s) [not to exceed 2 hours].

E-MAIL _____

The processing fee has been paid for through an unrestricted educational grant by Bayer Corporation.

TEAR OUT, FOLD, AND TAPE - DO NOT STAPLE

Off-Label Disclosure Statement

This educational activity contains discussion of published and/or investigational uses of agents that are not indicated by FDA. The faculty, Postgraduate Institute for Medicine, Health Management Solutions, Inc. or Bayer Corporation do not recommend the use of any agent outside of the labeled indications. Please refer to the official prescribing information for each product for discussion of approved indications, contraindications and warnings.

Disclaimer

Any procedures, medications, or other courses of diagnosis or treatment discussed or suggested in this activity should not be used by clinicians without evaluation of their patient's conditions and possible contraindications on dangers in use, review of any applicable manufacturer's product information, and comparison with recommendations of other authorities.