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## Current Treatments for Bipolar Disorder: A Review and Update for Psychologists

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Practicing psychologists are likely to be confronted with the diagnostic and treatment challenges associated with bipolar disorder, particularly the various classes of medication currently used in pharmacotherapy for the disorder. Although lithium remains a valuable resource, limitations associated with its use have prompted clinicians and researchers to explore the application of several different classes of agents, including anticonvulsants, calcium channel blockers, atypical antipsychotics, benzodiazepines and antidepressants, to the acute and long-term management of bipolar disorder. A review of these agents, as well as a summary of various psychotherapeutic modalities that can serve as adjunctive interventions to pharmacotherapy, is provided for psychologists.

The diagnosis and treatment of bipolar disorder remains a complex clinical issue. Despite its severity and chronicity, bipolar disorder frequently goes either undetected or misdiagnosed and is often inadequately treated. The disorder is associated with a high degree of burden and human suffering. In the past decade, bipolar disorder was ranked as the sixth leading cause of disability for individuals aged 15 to 44 years (Woods, 2000). One estimate of the annual cost to society produced by bipolar disorder totaled \$45 billion, with approximately \$8 billion being accounted for by suicide (Wyatt, Henter, Leary, & Taylor, 1995). The lifetime risk

of suicide for bipolar patients—at almost 19%—is the highest of any mental disorder (Goodwin & Jamison, 1990). Given the significant degree of morbidity and mortality associated with this illness, clinical and research activities have focused on identifying pharmacological and psychosocial interventions that would yield the greatest degree of therapeutic efficacy. Although lithium remains a valuable pharmacological resource for bipolar disease, several different classes of medications are now being utilized as either monotherapy or adjunctive treatment for various aspects of the illness. In the psychosocial sphere, an association between life

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stressors and onset of bipolar episodes has been clearly documented (Johnson & Roberts, 1995; Malkoff-Schwartz et al., 1998); consequently, psychosocial interventions are increasingly being recognized as an integral component of comprehensive treatment. Clinical and research opportunities exist for psychologists wishing to develop, implement, and monitor therapeutic interventions for bipolar disorder. The objective of this article is to provide psychologists with up-to-date diagnostic, pharmacologic, and psychotherapeutic information pertinent to the current conceptualization and treatment of bipolar disorder.

### Classification and Characteristics of Bipolar Disorder

Table 1 illustrates the position of bipolar disorder within the framework of the current classification system (American Psychiatric Association [APA], 2000). Essentially, bipolar disorder—previously referred to as manic-depressive illness—refers to a group of specific clinical syndromes, the predominant characteristic of which involves elevations or perturbations of mood accompanied by behavioral activation, impulsivity, disinhibition, or symptoms of hyperactivity or hyperarousal. A primary distinction among the bipolar disorders is the presence of either a *manic episode* or a *hypomanic episode*, the core features of which are presented in Table 2. A manic episode refers to a period (at least 1 week) of distinctly elevated, expansive, or irritable mood, in which three or more of the core manic symptoms have been present to a degree severe enough to produce psychosis, warrant hospitalization (to prevent harm to self or other), or produce marked impairment in social or occupational functioning (APA, 2000). A hypomanic episode involves elevated, expansive, or irritable mood that lasts at least 4 days and is noticeably different from the patient's usual euthymic mood. Three or more of the core symptoms listed in Table 2 must be present. The distinction between a manic episode and a hypomanic episode is one of severity: Although the mood disturbance produces a change in functioning that is observable by others, the symptoms are not severe enough to produce psychosis, necessitate hospitalization, or cause marked social or occupational impairment.

In order to diagnose *bipolar I disorder*, the clinician must establish the presence of one or more manic episodes in either the

patient's current or remote history. The criteria for bipolar I disorder can also be met if the patient is evidencing a *mixed episode*. This refers to a period of at least one week in which the patient is meeting criteria for both a manic episode and a major depressive episode (five or more symptoms of depressed mood, loss of interest or pleasure, significant changes in appetite, sleep disturbance, psychomotor agitation or retardation, loss of energy, feelings of worthlessness or excessive guilt, decreased concentration or decision-making capacity, and recurrent thoughts of death or suicidal ideation, plan, or intent; APA, 2000). Patients with mania who have never exhibited significant depression are still assigned a diagnosis of bipolar I disorder, based on the assumption that a depressive episode will develop at some point during the course of the illness (Dubovsky & Buzan, 1999). The lifetime prevalence of bipolar I disorder in the United States is approximately 0.4–1.6%, or roughly 1–3 million people (Evans, 2000). It tends to occur equally among men and women. Bipolar I disorder is a highly recurrent disorder, and it is estimated that at least 90% of individuals who exhibit a manic episode will go on to develop future episodes.

The diagnosis of *bipolar II disorder* is assigned to an individual who presents with a history of at least one hypomanic episode and who has had one or more episodes of major depression. There is no history of a manic or mixed episode. The prevalence of bipolar II disorder in the United States is approximately 0.5%, or roughly 2 million individuals, and the disorder seems to be more common in women than in men (Evans, 2000). A small percentage of bipolar II patients, 5–15%, will go on to exhibit a manic episode within the first 5 years of their illness, thereby changing their diagnosis to bipolar I disorder (APA, 2000). It should be noted that bipolar I and bipolar II can both demonstrate a particularly malignant course, referred to as *rapid cycling*, in which four or more mood episodes (e.g., manic, mixed, hypomanic, or major depressive) are exhibited within the span of a year. This course specifier is important to detect, as these patients have a differential response to standard pharmacotherapy and may be more resistant to treatment (Suppes, Dennehy, & Gibbons, 2000).

*Cyclothymic disorder* represents a distinct mood disorder, characterized by a more chronic course in which for at least 2 years, there have been numerous periods of hypomanic symptoms and numerous periods of depressive symptoms that do not meet criteria for a major depressive episode. During the first 2 years, there will have been no manic or mixed episodes. Prevalence rates for this disorder are estimated to be 0.4–1%, and there is a 15–50% chance that the individual with cyclothymic disorder will develop bipolar I or II disorder (APA, 2000). Patients who demonstrate manic or hypomanic symptoms but whose presentation or course of illness does not readily conform to the elements of the disorders listed above (e.g., recurrent hypomanic episodes in the absence of depressive symptoms) should be given a diagnosis of *bipolar disorder not otherwise specified* (NOS; APA, 2000). It is estimated that when cyclothymic disorder and bipolar disorder NOS are included in the group known as *bipolar spectrum disorders*, the prevalence for bipolar disorders increases to rates as high as 2.6–6.5% (Hirschfeld et al., 2000). Finally, the issue of *secondary mania* deserves mention. Manic-like symptoms that are produced by a general medical condition (e.g., multiple sclerosis, hyperthyroidism) are not diagnosed as either bipolar I or bipolar II; rather, these events are recorded as a *mood disorder due to a general medical condi-*

Table 1  
Classification of Mood Disorders

Bipolar disorder <sup>a</sup>	Depressive disorder <sup>b</sup>
Bipolar I	Major depressive disorder
Manic episode	Major depressive episode
Mixed episode	Dysthymic disorder
Bipolar II	Depressive disorder NOS
Hypomanic episode	
Cyclothymic disorder	
Bipolar disorder NOS	

*Note.* Categories are from the text revision of the *Diagnostic and Statistical Manual of Mental Disorders* (4th ed.; APA, 2000). Classification of mood disorders excludes those mood disorders that are due to a general medical condition or a substance. NOS = not otherwise specified.

<sup>a</sup> These disorders involve either depressive episodes or symptoms. <sup>b</sup> By definition, assigning a depressive disorder diagnosis indicates that there has never been a history of manic or hypomanic episodes or symptoms.

Table 2  
*Core Features of Mania and Hypomania*

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1. Inflated self-esteem or grandiosity
  2. Decreased need for sleep (e.g., feels rested after only 3 hr of sleep)
  3. More talkative than usual or pressure to keep talking
  4. Flight of ideas or subjective experience that thoughts are racing
  5. Distractibility (i.e., attention too easily drawn to unimportant or irrelevant external stimuli)
  6. Increase in goal-directed activity (either socially, at work or school, or sexually) or psychomotor agitation
  7. Excessive involvement in pleasurable activities that have a high potential for painful consequences (e.g., engaging in unrestrained buying sprees, sexual indiscretions, or foolish business investments)
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*Note.* From the text revision of the *Diagnostic and Statistical Manual for Mental Disorders* (4th ed.; APA, 2000).

*tion*, specifying the condition causing the disturbance. Similarly, manic-like symptoms that are due to the direct physiological effects of a substance—either a drug of abuse, a toxin, or a prescribed medication—are recorded as a *substance-induced mood disorder*, specifying the substance that produced the symptoms. It should be noted that mania or hypomania that is induced by antidepressant treatment is recorded as a substance-induced mood disorder.

Accurate diagnosis and assessment of bipolar disorder have proven to be a challenge, as issues relevant to early detection and intervention have increasingly become areas of focus. The mean age of onset of bipolar disorder tends to be mid-teens to early 20s, with the majority of patients exhibiting significant symptoms by the age of 25 (Evans, 2000). Early age of onset (e.g., prior to the age of 17) appears to be associated with a more severe course of illness (Suppes et al., 2000). Longitudinally, the duration between episodes, known as the interepisodic period, tends to be longer for the initial episodes and decreases as the illness progresses. The role of psychosocial stressors also seems to change over the course of bipolar disorder. Stressful life events seem to play a more instrumental and activating role in early episodes, with subsequent episodes arising more autonomously and in the absence of clear external precipitants (Johnson & Roberts, 1995). It has been speculated that the neurophysiological alterations underlying multiple episodes of mania may compromise the brain's capacity to sustain a stable state of euthymia (Suppes et al., 2000). A hypothetical model that involves the concept of kindling (elicitation of a response by a previously insufficient stimuli following repeated exposure to that stimuli) has proven valuable in conceptualizing the neuronal and neurochemical changes that may result from recurrent episodes and that may place patients at risk for a more malignant course (see Post, 1992).

In light of the potential neurophysiological changes, delayed treatment—produced by inaccurate or delayed diagnosis—can have a profoundly devastating impact (Hirschfeld et al., 2000); unfortunately, this delay appears to be more the rule than the exception (Woods, 2000). Bipolar disorder often goes undetected and undiagnosed for many years following the emergence of symptoms. The mean latency between onset of illness and initiation of treatment has been noted to be a minimum of 5 years, with some patients reporting as much as a 10-year delay (Evans, 2000). The complexity of the bipolar symptom pattern itself, coupled with

the presence of comorbid disease (e.g., substance abuse) and inaccurate history provided by patients themselves, prove to be factors interfering with rapid identification. Some patients with bipolar disorder may be misdiagnosed as having major depressive disorder (or unipolar depression). Depressive episodes in bipolar disorder are more subjectively distressing to patients and tend to last longer (relative to the typically briefer manic phase), prompting patients to seek treatment when they are depressed (Ghaemi, 2001). Consequently, clinicians are encouraged to actively review for specific symptoms of bipolar disorder (particularly with depressed patients) and explore conspicuous areas of functioning in order to more readily detect bipolar disease. The mnemonic DIGFAST has been suggested as an aid to remember the core symptoms of mania and hypomania that accompany the fundamental mood disturbance: *D*istractibility, *I*nsomnia, *G*randiosity, *F*light of ideas, *A*ctivities, *S*peech, *T*houghtlessness (referring to impulsive, risk-taking behavior; Ghaemi, 2001). If bipolar disorder is suspected, obtaining collateral information from family members or significant others—contingent on obtaining and documenting the proper authorization from the patient—is strongly recommended. Use of a screening tool during the initial diagnostic interview, such as the Mood Disorder Questionnaire (Hirschfeld et al., 2000), a brief, self-report inventory developed specifically to assess for bipolar disorder, will ensure systematic review and increase detection.

### Pathophysiology of Bipolar Disorder

Whereas the precise causal basis and pathophysiology of bipolar disorder are not yet fully understood, genetic, biological, and pharmacological investigations have provided data that have modestly furthered our understanding of the emergence and expression of the illness over the course of the affected individual's life. Ongoing investigation is being conducted to isolate the specific gene sequence that produces either a protective effect or a susceptibility for the illness, as well as to identify the nature and manner in which environmental events may trigger episodes. At a different level of analysis, the cellular and molecular aspects of the signaling networks that regulate gene expression and neural plasticity are being characterized more distinctly (see Manji & Lenox, 2000). In this arena, the focus has shifted from the activity of neurotransmitters in the neuronal synapse to the sequence of intracellular

events that are initiated by neurotransmitter binding and that involve second messengers.

Neuroanatomically, the limbic system and associated regions are thought to serve as the primary locus of dysfunction in mood disorders. Complex interconnections between limbic structures and brain stem nuclei (impacting neurotransmitter regulation) and the proposed involvement of the hypothalamic–pituitary axis (mediating neuroendocrine functioning) are thought to mediate the behavioral expression of mood disorders (Altschuler, Bartzokis, Grieder, Curran, & Mintz, 1998). Neurotransmitter dysregulation has represented a core component in pathophysiological theory of mood disorders for decades. Alterations in norepinephrine, dopamine, and serotonin—neurotransmitters that are highly interdependent and modulate other neurotransmitters and hormone systems—have served as successful concepts in developing therapeutic targets for pharmacological agents (Goodwin & Jamison, 1990). The involvement of acetylcholine in interacting with these neurotransmitters, as well as with intracellular second messenger systems, has also been posited (Fankhauser & Benfield, 1999). The roles of gamma-amino butyric acid (GABA), the main inhibitory neurotransmitter in the brain, and glutamate, an excitatory neurotransmitter, in the course of mood disorder have increasingly been the source of investigation, particularly in light of the fact that several agents used for bipolar disorder (e.g., carbamazepine) modulate their activity.

Within the neuron, signal transduction systems have become a primary area of interest. These intracellular networks are coupled to a membrane-bound receptor and mediate the process by which receptor activation by a neurotransmitter is converted to cellular responses. *G proteins* (a group of guanosine triphosphate binding proteins) are coupled intracellularly to the membrane receptors and transduce the initial signal by stimulating or inhibiting *second messenger systems* (neurotransmitters are the first messengers). Second messengers mediate downstream events, primarily by causing the addition or removal of charged phosphate groups—a process referred to as *phosphorylation*—to specific protein targets (e.g., a receptor, an ion channel; Lenox & Hahn, 2000). The change in the size and charge of the protein, by virtue of its now being phosphorylated, alters its conformation and consequently its function. For example, as a result of phosphorylation, an active receptor may be inactivated (and vice versa), or a closed ion channel may be opened (and vice versa; Hyman & Nestler, 1993). In this fashion, second messengers mediate a wide array of intracellular processes (e.g., regulating ion channels, neurotransmitter synthesis, gene expression). Two second messenger systems are of particular relevance to bipolar disorder: The *cyclic adenosine monophosphate* (cAMP) system and the *phosphoinositide* (PI) system (Fankhauser & Benfield, 1999). It has been hypothesized that G proteins may be hyperfunctional in manic patients, thereby causing dysregulation in the downstream effects of these systems (Manji & Lenox, 2000).

Finally, disruptions in extracellular and intracellular levels of the positively charged ion calcium have been implicated in the pathophysiology of bipolar disorder. Altered levels of extracellular calcium concentration have been associated with changes in mood, arousal, and cognition. Alterations in levels of calcium may be clinically manifested as mania, depression, irritability, psychosis, reduced consciousness, delirium, and possibly coma (Currier & Goodnick, 1998). Intracellularly, calcium is also linked to second

messenger systems that, when dysregulated, can result in mania (Fankhauser & Benfield, 1999). Through these systems, calcium ions regulate the synthesis and release of neurotransmitters (e.g., norepinephrine, dopamine, serotonin), neuronal excitability, and long-term changes that occur within the neuron (Manji & Lenox, 2000).

## Pharmacological Treatment of Mania

### *Lithium*

The most extensively studied mood-stabilizing agent, lithium remains the cornerstone and often the first choice of treatment for bipolar disorder. Although the precise mechanism of action is not yet fully understood, decades of research have allowed for considerable characterization as to the nature of its pharmacological activity (see Lenox & Hahn, 2000). At the neurotransmitter level, lithium impacts multiple systems, including dopamine (increasing turnover and decreasing synthesis), norepinephrine (initially increasing reuptake followed by reestablishing baseline levels), and serotonin and acetylcholine (enhancing neurotransmission of both of these systems; Lenox & Hahn, 2000). Furthermore, chronic lithium treatment appears to increase levels of the inhibitory transmitter GABA as well as to increase the uptake of the excitatory transmitter glutamate (resulting in less neurotransmitter in the synapse; Lenox & Hahn, 2000). At the intracellular level, lithium has been found to impact the cAMP system (partially by inhibiting stimulation of adenylyl cyclase) and the PI system (by inhibiting the production of inositol), thereby reducing responsiveness to neurotransmitters (Manji & Lenox, 2000). Lithium has also been found to decrease calcium transport into cells and to alter excretion by increasing the renal tubular reabsorption of calcium (Fankhauser & Benfield, 1999).

Lithium has traditionally been the most widely used agent for bipolar disorder, with established efficacy in controlling acute manic episodes and preventing or modulating subsequent episodes of mania. It was approved by the Food and Drug Administration (FDA) in 1970 for acute mania, and in 1974 it became the only agent to be approved for maintenance therapy (Nemeroff, 2000). An analysis of long-term data revealed that lithium treatment was found to be associated with a marked reduction in life-threatening suicidal acts (Tondo et al., 1998). Lithium, however, is not without its limitations. It has been estimated that approximately 20–40% of patients with acute mania fail to respond adequately to lithium (Tohen & Grundy, 1999). In longer-term follow-up, it has been observed that almost 40% of patients maintained on lithium have a recurrence of mania within 2 years after recovering from the acute episode (Harrow, Goldberg, Grossman, & Meltzer, 1991), and it is estimated that as many as 55% of patients will develop resistance to lithium after 3 years of treatment (Nemeroff, 2000). Furthermore, it is known that certain subtypes of bipolar disorder—namely, mixed episodes, rapid-cycling syndromes, and severe mania with psychosis—respond less favorably to lithium treatment (Bowden, 2000; Marangell, Yudofsky, & Silver, 1999).

Aside from the significant percentage of patients who fail to respond to either acute or maintenance therapy, lithium has a narrow therapeutic-to-toxic dose ratio, contributing to low tolerability (Bowden, 2000). Given the narrow therapeutic range of lithium, other medications taken concomitantly with lithium

should be evaluated for potential drug–drug interactions that could impact lithium levels (Marangell et al., 1999). Side effects include tremor, psychomotor slowing, weight gain, gastrointestinal discomfort, and neurocognitive impairment. Lithium's onset of action is slow, requiring 10–14 days after therapeutic serum levels are achieved, and patients receiving lithium must undergo regular monitoring of blood counts, metabolic panel, urinalysis, and thyroid function (Nemeroff, 2000). Consequently, in spite of lithium's proven efficacy, the observed limitations prompted clinicians and researchers to investigate the efficacy and safety of other classes of agents (see Table 3).

### Anticonvulsants

Anticonvulsant agents have increasingly come to represent important pharmacotherapeutic alternatives, either as monotherapy or as augmentation to lithium. The original rationale for their use in the treatment of mood disorders was based on observations made during epilepsy trials that these agents exerted therapeutic impact on mood stability and interpersonal functioning. Initially, anticonvulsants were used with patients who were resistant to standard treatments or whose symptoms were particularly acute, brittle, or difficult to manage in the long-term. However, these agents are increasingly being considered as first-line treatments in various algorithms for acute mania and maintenance therapy (see Goldberg, 2000). Compliance rates with the anticonvulsants have been found to be better than with lithium (Weiss et al., 1998).

*Valproate.* In 1995, valproate became the first anticonvulsant approved by the FDA for the treatment of mania. There are several preparations of valproate available in the United States, including valproic acid, sodium valproate, and the enteric-coated formulation, divalproex sodium (Marangell et al., 1999). Available as an antiepileptic drug in the United States since 1978, valproate has a broad spectrum of activity in various animal seizure models. The exact mechanism responsible for the drug's antimanic effect remains unknown, although it appears to be related to enhanced GABA activity by increasing its synthesis, inhibiting its degradation, and possibly potentiating GABA-mediated postsynaptic inhibition in a fashion similar to benzodiazepines (Dean, 1996). More recently, valproate was shown to interact with G proteins to exert effects on components of the cAMP-signaling system, although this is not yet fully understood (Manji & Lenox, 2000).

Valproate exhibits superior efficacy versus placebo and comparable efficacy with lithium in treating acute mania (Bowden et al., 1994; Pope, McElroy, Keck, & Hudson, 1991). Data compiled from several trials also support valproate's superior efficacy over lithium in the treatment of mixed mania and rapid cycling (Nemeroff, 2000); it is currently the mood stabilizer of choice for rapid-cycling presentations (Goldberg, 2000). Although data regarding efficacy for long-term treatment are limited, results from several studies suggest that valproate, both as monotherapy and in combination with lithium, decreases the likelihood of relapse or recurrence during maintenance therapy (Tohen & Grundy, 1999).

Valproate is generally well tolerated. It demonstrates a side-effect profile that is more favorable than that of lithium, contributing to better compliance rates (Tohen & Grundy, 1999; Weiss et al., 1998). Side effects include drowsiness, tremor (usually mild and transient), hair loss or alopecia, weight gain, and gastrointestinal discomfort, the most common side effect (Marangell et al., 1999). This latter side effect can be minimized by using the enteric-coated formulation, divalproex sodium. A significant advantage of valproate is the ability to rapidly administer loading doses that may produce a more rapid antimanic response (Dubovsky & Buzan, 1999). Several studies have indicated that a significant response with minimal side effects is observed as soon as 3 days following initiation of treatment with valproate (Keck, McElroy, & Strakowski, 1998). From a pharmacoeconomic perspective, this can translate into decreased lengths of hospital stays, as evidenced by at least one finding that patients treated with valproate left the hospital more quickly than those taking other mood-stabilizing agents (Frye, Altshuler, Szuba, Finch, & Mintz, 1996).

*Carbamazepine.* Although it has not yet received FDA approval for bipolar disorder, carbamazepine has considerable mood-stabilizing properties and has demonstrated efficacy in the treatment of mania. It figures prominently in several practice guidelines as either a first- or second-line intervention (Goldberg, 2000). Its mechanism of action remains to be fully elucidated, although several observed pharmacological aspects appear to produce its antimanic properties. Carbamazepine has been found to enhance GABA activity, decrease the release of glutamate, and block calcium influx (Fankhauser & Benefield, 1999). Data also suggest that carbamazepine inhibits the cAMP-signaling pathway and sub-

Table 3  
*Beyond Lithium<sup>a</sup>: Current Pharmacological Armamentarium for Bipolar Disorder*

Anticonvulsants	Calcium channel blockers	Atypical antipsychotics	Benzodiazepines	Antidepressants
valproate <sup>a</sup>	verapamil	olanzapine <sup>a</sup>	lorazepam	bupropion
carbamazepine	diltiazem	risperidone	clonazepam	paroxetine
lamotrigine	nifedipine	clozapine		fluoxetine
gabapentin	nimodipine	quetiapine		citalopram
topiramate		ziprasidone		sertraline
tiagabine				venlafaxine

*Note.* Drug names: valproate (Depakote); carbamazepine (Tegretol); lamotrigine (Lamictal); gabapentin (Neurontin); topiramate (Topamax); tiagabine (Gabitril); verapamil (Calan); diltiazem (Cardizem); nifedipine (Procardia); nimodipine (Nimotop); olanzapine (Zyprexa); risperidone (Risperdal); clozapine (Clozaril); quetiapine (Seroquel); ziprasidone (Geodon); lorazepam (Ativan); clonazepam (Klonopin); bupropion (Wellbutrin); paroxetine (Paxil); fluoxetine (Prozac); citalopram (Celexa); sertraline (Zoloft); venlafaxine (Effexor).

<sup>a</sup> Approved by the Food and Drug Administration for the treatment of acute mania.

sequently brings about long-term gene expression (Manji & Lenox, 2000).

Results from several double-blind, placebo-controlled studies indicate that carbamazepine is more effective than placebo and comparable to lithium in the treatment of acute mania (Keck et al., 1998; Marangell et al., 1999). Like valproate, carbamazepine has demonstrated efficacy in patients presenting with clinical features that are typically associated with poorer lithium response, such as mixed episodes, rapid cycling, or severe mania (Keck et al., 1998). Numerous studies have shown that in maintenance therapy, carbamazepine, either alone or in combination with lithium, has efficacy in the long-term prophylaxis of manic episodes (Marangell et al., 1999; Nemeroff, 2000).

As with lithium, carbamazepine requires gradual dose titration to reduce side effects. Given this, the onset of action typically ranges from 1 to 2 weeks; if no clinical improvement is seen within this time frame, alternative approaches should be considered. Side effects can range from mild to severe and may include sedation, ataxia, gastrointestinal distress, liver toxicity, hematologic disorders (e.g., agranulocytosis, aplastic anemia), and dermatologic rashes (including the severe Stevens-Johnson syndrome; Hebert & Ralston, 2001). Less than 50% of patients who are placed on carbamazepine are still taking this agent when assessed a year later, partially due to these side effects (Nemeroff, 2000). Carbamazepine is an inducer of the P450 isoenzyme 3A4, indicating that it may increase the metabolism of other medications (e.g., oral contraception), thereby decreasing their efficacy (Marangell et al., 1999).

*Newer anticonvulsants.* Data have begun to amass regarding the use of the second-generation anticonvulsants, such as lamotrigine, gabapentin, and topiramate, in the treatment of bipolar disorder, although these agents are still considered experimental. In practice guidelines, these agents do not yet occupy first- or even second-line intervention status (Goldberg, 2000). Rather, their use is most prominent for patients who have been refractory to other approaches, as well as for patients who present either with the rapid-cycling variant or during the depressed phase of the illness.

The potential for lamotrigine to positively impact mood was first noted in reports that seizure patients experienced more robust improvements in global well-being than in seizure control. Its mechanism of action is related to sodium channel blockade, which impacts calcium channels and decreases the release of glutamate (Fankhauser & Benefield, 1999). A double-blind, placebo-controlled study of 180 patients with rapid-cycling bipolar disorder demonstrated efficacy in maintaining euthymia for up to 6 months with lamotrigine as monotherapy versus placebo (Nemeroff, 2000). A literature review of case reports and open-label studies of lamotrigine, either as monotherapy or as adjunctive treatment, indicated a broad spectrum of efficacy for patients exhibiting mania, hypomania, and mixed and depressive episodes, as well as for patients refractory to other agents (Calabrese, Rapport, Shelton, Kujawa, & Kimmel, 1998). Lamotrigine appears to be well tolerated. Side effects include headaches, dizziness, gastrointestinal distress, blurred or double vision, and—the most significant—the possibility of Stevens-Johnson rash (Marangell et al., 1999).

Gabapentin, which enhances GABA while inhibiting the release of glutamate, may provide some benefit as adjunctive therapy for bipolar disorder, as there is little research demonstrating gabapentin's efficacy as monotherapy. Gabapentin is well tolerated and has

little interaction with other agents, making it attractive as an augmentation agent. Case reports or small open-label trials suggest that adding gabapentin to the primary mood stabilizer may yield additional benefit in bipolar depression, treatment of refractory patients, and maintenance therapy (Keck et al., 1998). However, results from a small placebo-controlled trial of adjunctive gabapentin for bipolar patients demonstrating residual symptoms, despite ongoing therapy with lithium or valproate, failed to find superior efficacy to placebo (Pande, Crockatt, Janney, Werth, & Tsaroucha, 2000).

Topiramate represents another agent in this class that, like gabapentin, has preliminary data suggesting benefit as adjunctive therapy for mania, hypomania, and mixed episodes (Marcotte, 1998). However, a review of several studies suggests that compared with the other newer anticonvulsants, topiramate may exert a negative effect on cognitive functioning (Goldberg & Burdick, 2001). Conversely, an advantage that is relatively unique to topiramate is that of weight loss associated with its use; adding it as an adjunctive agent to standard therapies may counteract weight gain produced by those agents (Nemeroff, 2000).

### *Calcium Channel Blockers*

This class of agents has demonstrated some efficacy in the treatment of acute mania, although they do not figure prominently in the available practice guidelines as either first- or second-line interventions (Goldberg, 2000). Nonetheless, there is a small literature on the application of calcium channel blockers to acute mania, rapid-cycling presentations, and in long-term prophylaxis. The direct mechanism of action is inactivation of calcium channels in order to block calcium influx. This leads to inhibition of neural signal transmission and neurotransmitter synthesis and release (Currier & Goodnick, 1998). The first case report of the use of the calcium channel blocker verapamil for acute mania appeared in the literature in 1982 (Dubovsky, Franks, Lifschitz, & Coen, 1982). Since then, several small double-blind trials have found verapamil, as well as other calcium channel blockers (e.g., diltiazem, nifedipine, nimodipine), to have antimanic efficacy (Marangell et al., 1999). For prophylaxis, there appears to be some evidence for the role of verapamil in the maintenance therapy for bipolar patients (Giannini, Taraszewski, & Loiselle, 1987).

### *Atypical Antipsychotics*

Given the finding that as many as two thirds of bipolar patients have a lifetime history of psychosis, it is not surprising that these patients will receive antipsychotic medications during the acute phase of treatment; however, approximately one third of bipolar patients go on to receive antipsychotic agents in combination with a mood stabilizer during the maintenance phase as well (Tohen & Zarate, 1998). When used for acute intervention, the antipsychotics clearly serve to decrease agitation, disorganization, and violence and/or psychosis while the mood-stabilizing agent is taking effect; the role that these agents have in the longer-term maintenance phase of treatment remains to be clarified through longitudinal studies. Whereas the traditional or conventional antipsychotics have been used for several decades, the newer atypical antipsychotics—so called for their novel pharmacologic profiles and decreased tendency to produce extrapyramidal side effects—are

receiving increased attention due to their improved tolerability and reduced side effects. In addition, data suggest that these agents may have antidepressant and mood-stabilizing properties (Tohen & Grundy, 1999), possibly through increased activity within the serotonergic system. A recent naturalistic review of three atypical antipsychotics—clozapine, risperidone, and olanzapine—indicated that all three agents demonstrated equivalent efficacy in treating bipolar disorder but were differentiated by their side-effect profiles (Guille, Sachs, & Ghaemi, 2000).

**Olanzapine.** Olanzapine recently became the first atypical antipsychotic to be approved by the FDA for the treatment of acute mania. Tohen and colleagues (Tohen et al., 1999) randomized 139 acutely manic patients to either olanzapine or placebo and found that olanzapine was superior to placebo for decreasing manic symptoms. In a direct head-to-head comparison with lithium, 30 manic patients were randomly assigned to either olanzapine or lithium treatment (Berk, Ichim, & Brook, 1999). Following 4 weeks of treatment, there were no significant differences in efficacy between the two groups. Adding olanzapine to a mood stabilizer was also found to be effective in patients who had been refractory to two prior treatment strategies (McElroy et al., 1998). Other small trials or case reports suggest that olanzapine may be effective for patients exhibiting mixed episodes. Side effects noted from trials include somnolence, dry mouth, dizziness, and weight gain (Tohen et al., 1999). The weight gain appears to be a significant issue, particularly in light of the fact that the primary mood stabilizers also evidence this propensity. This may be a limiting factor for using olanzapine in combination with other agents (Guille et al., 2000). Interestingly, there have been approximately 10 reports in the literature of olanzapine precipitating or inducing a manic or hypomanic episode, possibly related to its effects on the serotonin system (Aubry, Simon, & Bertschy, 2000).

**Risperidone.** Several studies support the efficacy of risperidone for acute mania, either in monotherapy or as an adjunctive agent (see Ghaemi, 2000). Segal, Berk, and Brook (1998) conducted a double-blind, placebo-controlled trial directly comparing risperidone and lithium in the treatment of mania. Results indicated that both agents demonstrated equal efficacy. Preliminary data suggest that as an adjunctive therapy, risperidone may provide long-term mood-stabilizing effects (Ghaemi, 2000). Results from a large, open-label study with 541 patients indicated that adding risperidone to a mood stabilizer produced highly significant improvement in mood symptoms over a 6-month period (Vieta et al., 2001). Like olanzapine, risperidone use has been reported to induce mania or hypomania; caution and monitoring for this effect should therefore be exercised when initiating treatment (Aubry et al., 2000).

**Clozapine.** Clozapine has been associated with relatively rapid amelioration of manic symptoms and efficacy with mixed episodes, rapid cycling, and refractory mania (Keck et al., 1998). A review of 10 reports in which clozapine, either as monotherapy or in conjunction with other agents, had been used for treatment-refractory bipolar patients indicated that 71% of patients demonstrated significant improvement and maintained this improvement over time (Zarate, Tohen, & Baldessarini, 1995). A more stringent review of prospective studies identified 3 studies, one randomized, all of which supported clozapine's likely effectiveness for mania (Ghaemi, 2000). Despite this promising data, clozapine's tendency to produce agranulocytosis (reduced white blood cell count) is

cause for concern and prevents it from being considered as a first-line agent within this class.

**Quetiapine and ziprasidone.** To date, few reports appear in the literature regarding the use of the two other atypical antipsychotics—quetiapine and ziprasidone—to bipolar disorder. Results from studies involving a small number of patients have provided preliminary support for quetiapine in acute mania (Dunayevich, Tugrul, & Strakowski, 2001) and rapid-cycling presentations (Ghaemi, Goldberg, & McNally, 2001). Case reports suggest that quetiapine may be useful for some patients who have been resistant to other agents (Ghaemi & Katzow, 1999). This was recently corroborated by a prospective, open-label study in which 10 bipolar patients who had been suboptimally responsive to other mood stabilizers demonstrated significant improvement on quetiapine (Sajatovic et al., 2001). One report in the literature suggests that ziprasidone, the most recent in the atypical antipsychotics to be introduced to the U.S. market, may demonstrate efficacy in acute mania, bringing about rapid stabilization by the second day of a 3-week, placebo-controlled trial (Keck & Ice, 2000). Pharmacologically, ziprasidone exhibits some reuptake blockade of serotonin and norepinephrine, representing a theoretical concern for mania induction, although there have been no reports of this to date.

### *Benzodiazepines*

The role of benzodiazepines for bipolar disorder warrants mention, not because of their mood-stabilizing properties but because of their use for behavioral control during acute mania (Marangell et al., 1999). Benzodiazepines—primarily lorazepam and clonazepam—provide a more benign alternative to antipsychotic agents for attenuating symptoms such as agitation, insomnia, anxiety, and hyperactivity while waiting for the mood stabilizer to take effect. It has been speculated that the anticonvulsant property of benzodiazepines—enhancing GABA transmission—may contribute to the antimanic response (Fankhauser & Benfield, 1999). In addition, there is evidence that restoration of sleep produced by a benzodiazepine may foster a more rapid resolution of mania (Nowlin-Finch, Altshuler, Szuba, & Mintz, 1994). There is little evidence for the utility of benzodiazepines in long-term management of bipolar disorder.

### Treatment of Bipolar Depression

The clinical characteristics of bipolar depression (defined as an episode of major depression experienced by a patient who has met criteria for either bipolar I or bipolar II disorder) may be somewhat different than those for unipolar major depression. One recent study comparing patients with bipolar depression versus patients with unipolar depression noted that, although the severity of depression was equivalent across both groups, the bipolar group presented with more psychomotor retardation, more melancholia, more atypical features (e.g., hypersomnia), and a history of psychosis during prior episodes of depression (Mitchell et al., 2001). Furthermore, it appears that the most prominent feature of rapid-cycling bipolar patients, a group that is generally more treatment-resistant, is frequent and recurrent depressive episodes that are distinctly severe and a challenge to manage (Calabrese et al., 2001). The greatest clinical concern produced by bipolar depres-

sion is the increased risk of suicidal behavior associated with this phase of the illness, representing the need for expeditious and effective intervention. The treatment of bipolar depression also needs to be conceptualized differently than the treatment of unipolar depression. The depressive phase of bipolar disorder appears to be less responsive to standard treatments than the manic phase, with the primary challenge being to ameliorate depressive symptomatology without precipitating a manic episode (Compton & Nemeroff, 2000).

In bipolar depression, it has been recommended that the first pharmacological intervention be to initiate or maximize a mood stabilizer rather than to start an antidepressant (Marangell et al., 1999). Expert guidelines indicate that lithium monotherapy is the preferred first-line agent for the depressive phase of bipolar disorder (Goldberg, 2000). Among the anticonvulsants, valproate appears to be the first-choice agent, either as monotherapy or adjunctively to lithium. The efficacy of lamotrigine as monotherapy was investigated in a double-blind, placebo-controlled study of 192 patients with bipolar I depression (Calabrese, Sachs, Ascher, Monaghan, & Rudd, 1999). Results indicated that lamotrigine was effective and well-tolerated, with improvement in depressive symptoms being seen as early as the third week. Results from a recent study in which lamotrigine was used as maintenance therapy for patients with rapid-cycling bipolar II disorder indicated that this agent may be effective in alleviating depression with this challenging population (Calabrese et al., 2001). Preliminary data suggest that gabapentin may be effective as an adjunctive agent for bipolar depression (Compton & Nemeroff, 2000).

### *Antidepressants*

There has been some recent attention and controversy generated toward the application of antidepressants to the treatment of bipolar depression. In general, the use of antidepressants with this population has been associated with two risks: Induction of acute mania and initiation of a long-term pattern of rapid-cycling episodes (representing a more severe course of illness; Ghaemi, 2000). Retrospective reviews suggest that the rate of mania induction may be as high as one third for patients receiving antidepressant treatment, with one fourth of patients demonstrating the activation of a rapid-cycling course (Goldberg, Harrow, & Grossman, 1995). The risk of induced mania may be higher for depressed patients with bipolar disorder who present with a prior history of rapid-cycling or severe manic episodes (Boerlin, Gitlin, Zoellner, & Hammen, 1998). Given these risks, initiation of antidepressant therapy in the setting of bipolar disorder should be conducted with caution, particularly in light of the fact that controlled studies have failed to find clear additional benefit to adding an antidepressant to lithium versus the use of lithium alone (Ghaemi, 2000). Nemeroff et al. (2001) recently found that the addition of either paroxetine or imipramine to depressed bipolar patients taking lithium did not increase antidepressant efficacy for those patients exhibiting high serum lithium levels. However, for patients with low serum levels of lithium, augmentation with an antidepressant did reduce depression (compared with adding a placebo to the lithium regimen; Nemeroff et al., 2001).

When antidepressant treatment is deemed to be clinically appropriate (possibly after poor response to a mood stabilizer alone), expert guidelines seem to favor the use of bupropion, followed by

the SSRIs, particularly paroxetine (Goldberg, 2000). Other antidepressants found to be appropriate include fluoxetine, sertraline, citalopram, and venlafaxine. Nefazodone and mirtazapine have not yet been well-studied. When used for bipolar depression, the dosing schedule for antidepressants is similar to that for unipolar depression. However, treatment duration tends to be briefer; guidelines recommend that antidepressants be discontinued within 3–6 months of remission of depressive symptoms in order to minimize the risk of inducing mania. Goldstein et al. (1999) reported on 6 patients who paradoxically demonstrated activation of mania during antidepressant discontinuation, suggesting that tapering patients off antidepressants should proceed cautiously and slowly, pending controlled investigation of this preliminary report. Although long-term use of antidepressants is commonly seen in clinical practice, the efficacy and safety of such long-term use in bipolar disorder have not been empirically established (Ghaemi, Lenox, & Baldessarini, 2001). For example, maintenance treatment with an antidepressant, particularly in the absence of a mood stabilizer, has been shown to double the rate of manic episodes (Boerlin et al., 1998). However, the point has recently been made that the decision to discontinue antidepressants to reduce the risk of mania induction needs to be weighed against the risk of a depressive relapse (Altshuler et al., 2001).

### *Combination Therapies*

Presently, a broad-spectrum medication that is effective during acute and maintenance therapy is not yet available, indicating that many patients will require a complex combination of different medications during different phases of the illness. Given the range of symptoms and the heterogeneous subtypes of the disorder, the challenge to the prescribing clinician becomes quite apparent. Side effects, potential drug toxicity, and possible drug interactions complicate treatment and management further. Studies are needed that examine the safety and efficacy of polypharmacy for bipolar disorder. For example, one review of combination treatment suggests that lithium and an anticonvulsant, particularly valproate, is the safest and most efficacious combination treatment (Freeman & Stoll, 1998). Post, Frye, Leverich, and Denicoff (1998) also reviewed combination strategies and offered rationales for implementing various mood-stabilizing agents in conjunction. These authors noted the necessity for a database that can systematically guide decision making for drug selection and polypharmacy.

### *Review of Psychosocial Interventions*

Although pharmacotherapy represents the primary treatment for bipolar disorder, augmentation with various psychotherapeutic techniques is now being recommended by practice guidelines. Goals of psychotherapy are broad and varied, but a primary target is that of reducing the alarmingly high rates of medication discontinuation and overall noncompliance with pharmacological regimen. Risk factors that are associated with mood instability also serve as targets for psychotherapeutic interventions. These include marital conflicts, work-related difficulties (including unemployment), family stress, and heightened levels of expressed emotion (hostility, negative criticism, or emotional overinvolvement; Rothbaum & Astin, 2000). Consequently, goals of psychotherapy frequently involve enhancing social and occupational functioning,

recruiting family and spouse support as appropriate, and generally identifying psychosocial stressors that may trigger mood episodes. Despite these fertile areas, psychotherapy has not received much attention until recently. Over the last several years, various forms of adjunctive psychotherapy have been developed for bipolar disorder, including cognitive-behavioral, interpersonal, psychoeducational, and family therapies (see Craighead, Miklowitz, Vajk, & Frank, 1998). For many of these treatments, manuals and conceptual articles have been published (Basco & Rush, 1996; Frank et al., 1994; Miklowitz & Goldstein, 1997; Scott, 1996); the availability of these manuals enables practitioners to apply these treatments in a fashion sufficiently standardized so as to produce effective interventions.

### *Family and Marital Treatment*

Family and marital treatments have received attention, in part due to evidence that expressed emotion is a powerful trigger of relapse in bipolar disorder. One approach, family focused treatment (FFT) for bipolar disorder (Miklowitz & Goldstein, 1997), is an adaptation of an intervention that has been successful for schizophrenia. The goal of treatment is to improve family functioning through a combination of communication and problem-solving training, along with providing education regarding the illness.

Following up on positive results from an earlier study, Miklowitz and colleagues (Miklowitz et al., 2001) conducted a study in which 101 patients were randomly assigned to a 1-year program of FFT plus medication management or crisis management with naturalistic follow-up (CMNF). Results indicated that patients who received FFT achieved longer periods without relapse than patients assigned to CMNF. The greatest treatment effects were noted for depressive symptoms. In addition, after 9 months of FFT, patients and family members were assessed and were shown to be using more positive communication than those in CMNF; this improvement appeared to predict symptomatic amelioration (Simoneau, Miklowitz, Richards, Saleem, & George, 1999). Other researchers have shown that multifamily groups have led to a decrease in the frequency of expressed emotion among families of individuals with bipolar disorder (Honig, Hofman, Rozendaal, & Dingemans, 1997). Finally, psychoeducation for spouses of patients with bipolar disorder has been compared with psychoeducation provided alone to the patient (Clarkin, Carpenter, Hull, Wilner, & Glick, 1998). Results suggested that psychoeducation for spouses led to a significant improvement in patients' level of social adjustment and global functioning, even though no effect was noted on specific symptoms.

### *Group Approaches*

Various group therapy modalities have been formulated and implemented with varying degrees of success with patients with bipolar disorder (see Rothbaum & Astin, 2000). The Life Goals Program, a structured, manual-based group therapy program, has been developed and recently examined to determine whether the procedures could be readily taught to therapists, as well as to determine therapeutic impact on patients (Bauer, McBride, Chase, Sachs, & Shea, 1998). The program consists of Phase 1 (5 weekly sessions of structured psychoeducation) and Phase 2 (behavioral

strategies to tackle a social, occupational, or leisure goal that has been disrupted by bipolar disorder). Individually tailored goals range from simple (e.g., getting a driver's license) to complex (e.g., returning to employment). The program can be replicated by therapists and can be tolerated and used by patients (Bauer et al., 1998).

### *Individual Approaches*

*Interpersonal Psychotherapy and Social Rhythm Therapy (IPSRT).* IPSRT is a modification of Interpersonal Psychotherapy for Depression (IPT), which focuses on strategies for addressing unresolved grief, interpersonal disputes, interpersonal deficits, and role transitions (Frank et al., 1994). IPSRT incorporates behavioral interventions based on the supposition that certain life events may trigger episodes by disrupting stable activities or time cues (e.g., regular times for sleep, meals, exercise, and work). Studies conducted with IPSRT indicate that it can bring about increased stability in routines and daily rhythms (Rothbaum & Astin, 2000).

*Early symptom identification.* On the basis of evidence that bipolar episodes begin with idiosyncratic but consistent prodromal symptoms, Perry, Tarrier, Morriss, McCarthy, and Limb (1999) taught patients to identify early symptoms of relapse and to develop a personalized treatment-seeking plan. A reminder of this plan was laminated so that patients could carry it in their wallets. In the first randomized, controlled trial ( $N = 69$ ), this program led to a significantly longer time to relapse, as well as to improvements in social functioning and employment at an 18-month follow-up, compared with routine care (Perry et al., 1999).

*Cognitive-behavioral treatment (CBT).* Given its standardized techniques, CBT lends itself well to treatment of bipolar disorder, and studies are available to serve as guidelines for application (Basco & Rush, 1996). Beyond the need to challenge cognitions that may activate episodes of mania or depression, CBT can also target cognitions related to pharmacological compliance. Although data from larger, controlled trials in which CBT has been specifically applied to bipolar disorder are needed, the available literature supports application of this technique (see Scott, 1996). Fava, Bartolucci, Rafanelli, and Mangelli (2001) recently reported on the application of CBT to a small series of patients being treated with lithium for bipolar disorder. They found that CBT was associated with a significant reduction of residual symptomatology and demonstrated potential for enhancing lithium prophylaxis.

*Approaches in development.* Wehr et al. (1998) reported a case study in which bed rest for 14 hours per day was used to stabilize a bipolar patient with a rapid-cycling course. This has been replicated in another case (Wirz-Justice, Quinto, Cajothen, Werth, & Hock, 1999). In another novel approach, Davidoff, Forester, Ghaemi, and Bodkin (1998) videotaped a patient's initial hospitalization behavior, later showing the tape to the patient in order to enhance insight. Although very preliminary, these approaches warrant ongoing investigation to determine their utility as adjunctive interventions.

### Summary

Practicing psychologists should be very familiar with the diagnostic and therapeutic complexities associated with bipolar disorder.

der. Information reviewed here regarding its pharmacological management should provide an overview of the different classes of medications, as well as the strengths and limitations demonstrated by each class. Clearly, this remains a difficult disorder to manage pharmacologically. Pending the development of a broad spectrum agent that demonstrates efficacy in stabilizing acute episodes and reducing future recurrence of mania or depression, combination therapy with two or more agents will be the most likely scenario. The role of psychotherapy as adjunctive treatment for bipolar disorder has increased in prominence, and psychologists should familiarize themselves with the approaches noted above in order to provide appropriate care. Controlled investigations are needed to empirically determine which psychosocial approaches demonstrate the greatest efficacy.

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