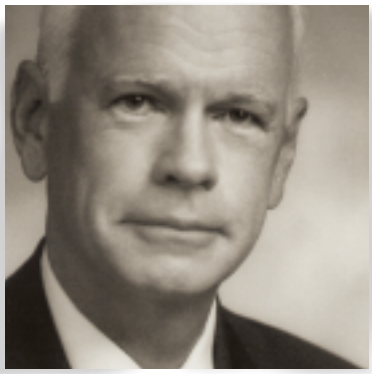
# *Bipolar disorder*

*Frederick K. Goodwin, MD; S. Nassir Ghaemi, MD*



Frederick K. GOODWIN

**From:** the Center on Neuroscience, Medical Progress, and Society Department of Psychiatry, George Washington University, Washington DC, USA (Dr Goodwin); and the Department of Psychiatry, Harvard Bipolar Research Program, Massachusetts General Hospital, Harvard Medical School, Cambridge, Mass, USA (Dr Ghaemi)

To approach the state of the art in diagnosis and treatment of bipolar disorder requires a review of the current state of both research and practice. There is no doubt that bipolar disorder has been an especially important and illustrative field of research in the evolution of psychiatry. Consider the history of the discovery of lithium. It is a classic example of an alert investigator with both basic science and clinical interests seeing the potential of an unexpected laboratory observation. Recent diagnostic research, in which controversy abounds regarding underdiagnosis and misdiagnosis of bipolar disorder, illustrates the richness of the clinical relevance of contemporary diagnostic and nosological research. Other aspects of current research that are relevant to diagnostic validity include genetic and outcome research. With respect to treatment, there are controversies regarding the use of mood-stabilizing agents, and dilemmas in the use of antidepressant agents in bipolar disorder. In terms of theories of the pathogenesis of bipolar illness, neurobiological research and theories have advanced, with the kindling hypothesis in particular seeming useful as a general theory of the pathophysiology of bipolar disorder. In addition, integrative research that includes attention to the psychosocial aspects of bipolar disorder appears on the verge of full development.

*Bipolar disorder's unique combination of three characteristics—clear genetic diathesis, distinctive clinical features, early availability of an effective treatment (lithium)—explains its special place in the history of psychiatry and its contribution to the current explosive growth of neuroscience. This article looks at the state of the art in bipolar disorder from the vantage point of: (i)* ***genetics*** *(possible linkages on chromosomes 18 and 21q, polygenic hypothesis, research into genetic markers); (ii)* ***diagnosis*** *(new focus on the subjective aspects of bipolar disorder to offset the current trend of underdiagnosis due to overreliance on standardized interviews and rating scales); (iii)* ***outcome*** *(increase in treatment-resistant forms signaling a change in the natural history of bipolar disorder); (iv)* ***pathophysiology*** *(research into circadian biological rhythms and the kindling hypothesis to explain recurrence); (v)* ***treatment*** *(emergence of the anticonvulsants, suggested role of chronic antidepressant treatment in the development of treatment resistance); (vi)* ***neurobiology*** *(evaluation of regulatory function in relation to affective disturbances, role of postsynaptic second-messenger mechanisms, advances in functional neuroimaging); and (vii)* ***psychosocial research*** *(shedding overly dualistic theories of the past to understand the mind and brain as an entity, thus emphasizing the importance of balancing the psychopharmacological and psychotherapeutic approaches). Future progress in the understanding and treatment of bipolar disorder will rely on successful integration of the biological and psychosocial lines of investigation.*

**Keywords:** *bipolar disorder; manic-depressive illness; mood disorder; depression; research; diagnosis; treatment; genetics; neurobiology; outcome*

**Address for correspondence:** Dr Goodwin, Department of Psychiatry, George Washington University, 2150 Pennsylvania Ave, NW, 8th Floor, Washington, DC 20037, USA (e-mail: psyfkg@gwumc.edu)

## Progress in scientific psychiatry: the central role of bipolar disorders

Bipolar illness, among psychiatric conditions, has served a central role in advancing clinical psychiatry, especially the interaction of biological predisposition with environmental stress. For one thing, there is a clear genetic diathesis for bipolar illness. Also, there are six different clinical state changes that can be studied: two states (depression and mania), and four phase changes (from depression to mania, from mania to depression, from depression to mixed states, and from mixed states to depression). These multiple clinical features of bipolar illness have served as a powerful research tool. And, as noted, there is substantial new bearing on the role of psychosocial factors in the emergence of episodes of affective illness (eg, the kindling paradigm) and in its treatment as well.

Despite the advances that have been made in research into affective illness, such progress is not necessarily smooth and rational. Unfortunately, there is also a tendency toward scientific fads, or "make-believes" according to van Praag.[1] It is unfathomable why certain areas of literature simply drop out as others capture our attention and take over. For example, the relatively robust literature on electrolyte disturbances died out rather abruptly in the late 1960s for no apparent reason. Certainly, there was no rash of nonreplications to explain the curious disappearance of this trail. Yet, research into bipolar disorder has nonetheless played an important role in hastening growth of psychiatric knowledge. The best example may be lithium and its presence at the creation of the psychopharmacological revolution.

## The psychopharmacological revolution: lithium as a case example

John Cade, an Australian physician, tested a hypothesis he developed while interned in a Japanese POW camp during the Second World War: he hypothesized that mania and depression represented abnormalities of nitrogen metabolism. To test the behavioral effects of urea, a nitrogenous product in urine, in animals, he needed a soluble form of it; he found that the lithium salt of urea was appropriately soluble and when he gave it to guinea pigs, he found that it calmed them without sedation. While he assumed this was due to the urea, he was careful enough to try a different form of lithium just to be sure the calming effect was not due to lithium. Of course, he discovered that the effect *was* due to lithium. Realizing that the existing treatments for mania essentially put patients to sleep, he reasoned that lithium might calm mania without knocking them out and so he tried it in manic patients. While his early patients struggled with lithium toxicity, Cade had made a major discovery. Later, Cade's preliminary observations were replicated and considerably extended in controlled studies by Schou and his colleagues, and the rest is history.[2]

The story of lithium and mania provides a paradigm for a process that was repeated with the introduction of neuroleptics for schizophrenia and tricyclic agents for depression in the 1950s and the 1960s. The psychopharmacological revolution, which took shape with the development of those drugs, spawned three subrevolutions. First, there was a conceptual revolution; the effectiveness of medications implied that biological factors were involved in these illnesses and were indeed relevant to understanding them. Second, a methodological revolution ensued; psychopharmacological research required reliable diagnoses, and the work that led to DSM-III and DSM-IV (Diagnostic and Statistical Manual of Mental Disorders IIIrd and IVth editions) stemmed from this need. Initially, new diagnostic criteria were developed among the neo-Kraepelinian school at the Washington University in St Louis (Eli Robins, Samuel Guze, George Winokur), which laid the basis for the Research Diagnostic Criteria (RDC). After nearly a decade of research on the basis of these criteria, sufficient data had been obtained to support the wholesale reform of psychiatric diagnosis, which DSM-III represented. The publication of DSM-III in 1980 marked the arrival of a new scientific psychiatry; all this had originated in the psychopharmacological revolution. Finally, psychopharmacology played a substantial role in fueling the explosive growth of neuroscience, since the introduction of new medications led to research into their mechanisms of action. Thus, the understanding of central nervous system synaptic function grew largely from efforts to understand the mechanism of action of tricyclic antidepressants, neuroleptics, and lithium.

## The state of the art: diagnostic validity

The aim of sharper diagnosis remains an important goal for research in bipolar disorder today. Forty years ago, Robins and Guze[3] proposed that the diagnostic validity of psychiatric disorders rested on the proposition that clinical phenomenology should have a predictable relationship to

genetics, course, and treatment response. With respect to bipolar disorder, what is the state of the art in each of these areas? While our accumulated knowledge about manic-depressive illness in these four fields of research is indeed impressive, we face a paradox. Despite all we know, bipolar illness too often remains unrecognized or misdiagnosed, and inappropriately or ineffectively treated. Robins and Guze's criteria can serve as springboards to comment on the contemporary understanding of this fascinating and challenging illness.

## Clinical phenomenology

Clinical phenomenology is the framework that supports most other research. Is manic depressive illness a valid syndrome? Some[4,5] doubt that we can distinguish it from schizophrenia. However, in our opinion, the Kraepelinian model appears well supported by methodologically sound research.[6-8] To further solidify the current model, future work should focus on schizoaffective disorder and the validity of presumed subtypes of bipolar disorder, such as pure vs mixed mania.

Future diagnostic validity studies should also seek to sharpen the reliability of diagnostic criteria and clarify discrepancies in prevalence estimates. There appears to be a "coarsening of diagnosis"[1] in clinical practice and research that may confuse these issues. Particularly with respect to bipolar disorder, the subtleties of the diagnostic process are often ignored in the effort to avoid incorrectly labeling someone with the diagnosis. Thus, bipolar disorder tends to be underdiagnosed, with even episodes of pure mania being completely missed by clinicians (not to mention mixed mania, hypomania, or bipolar depression). In a recent review of diagnostic patterns in the community,[9] we and our colleagues found that about 60% of the hospitalized patients we diagnosed with bipolar disorder had received that diagnosis from previous psychiatrists. While this may not simply be an issue of diagnostic reliability, part of this diagnostic disagreement represents clinician disagreement. Similar diagnostic difficulties exist in the clinical interview of paranoid patients (thus making it difficult to diagnose some types of schizophrenia, schizoaffective disorder, psychotic depression, and borderline personality disorder). As Leston Havens has remarked,[10] perhaps diagnosis in psychiatry is in a stage similar to medicine before the advent of auscultation. Sophisticated clinical interviews, such as those developed by Harry Stack Sullivan,[11] Havens, and others, may be similar to auscultation, allowing us to see and hear what we otherwise would miss. This level of subtlety in the clinical interview is often difficult to achieve, much less standardize and teach for research purposes. As van Praag again notes, "one can witness a standardized interview degenerating into a question-and-answer game: answers being taken on face value, not caring for the meaning behind the words, disregarding the as-yet-unspoken and oblivious to the emotional content of the communication….There is the danger of the desk researcher studying rating scale and standardized interview results rather than actual patients. These may be data collected not by himself, but by a research assistant with little psychiatric experience and training."[1]

These observations could explain some of the contradictory results found with our current research tools. In nosology, these contradictory results are most relevant to the Epidemiological Catchment Area (ECA) and National Comorbidity survey, which sought to assess psychiatric illness in the general population of the US. The ECA study used the Diagnostic Interview Schedule (DIS) based on DSM-III, administered by trained lay people. Despite reliability studies with clinicians before the study, clinician-administered research interviews on the actual study population correlated poorly with DIS-based diagnoses in one of the ECA sites.[12] As shown in *Figure 1(next page)*, the best diagnostic agreement, with alcoholism, was only mild ($\kappa$=0.35), and it was worse with more diagnostically complex conditions like schizophrenia, depression, and (especially) mania. More recently, ECA-like diagnostic methods were used in the National Comorbidity survey; even with similar methods, the prevalence of mania was twice as high as in the ECA study (1.6% vs 0.8%) and the prevalence of unipolar depression was much higher (17% vs 8%).[13,14] On the other hand, rediagnosis of a subsample in that study by clinician researchers reported lower rates of nonaffective psychosis diagnosis than those made by lay interviewers.[15] These studies support the notion that such research techniques lead to a "coarsening of diagnosis," which makes for less reliable and possibly less valid results.

We would also suggest that attention to subjective aspects of psychiatric syndromes is important if diagnostic skills are to improve. One of the reasons that subjective phenomena are little studied is that they are deemed unmeasurable in a standardized way. But this is not the case. An excellent example is insight, the phenomenon of awareness of illness, pathological symptoms, or psychosocial sequelae of illness. This subjective phenomenon has recently been the subject of sophisticated research, with the creation of multiple standardized rating instruments[16-19] and a number of studies have quantified the impairment of insight in psychotic and mood

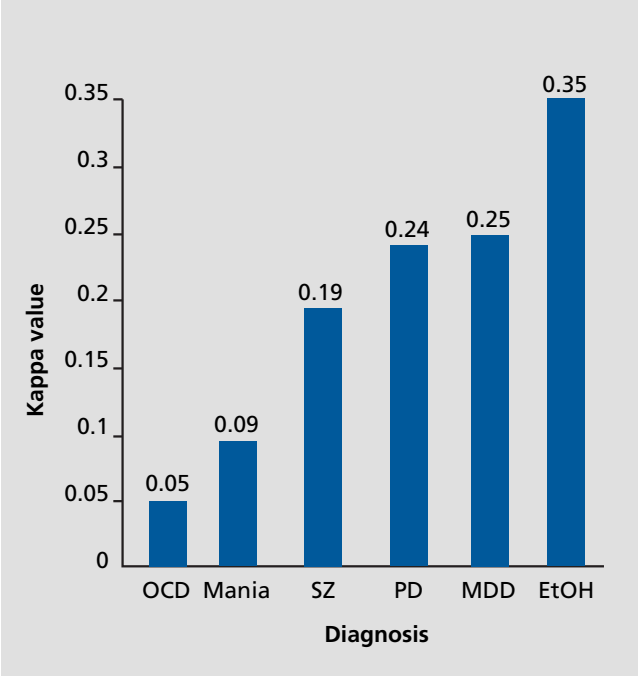



**Figure 1.** Agreement (kappa) of lay-administered Diagnostic Interview Schedule (DIS) diagnoses with clinician-researcher diagnoses (from the Epidemiological Catchment Area [ECA] study Baltimore site. EtOH, alcohol use disorders; MDD, unipolar major depressive disorder; OCD, obsessive-compulsive disorder; PD, phobic disorders; SZ, schizophrenia. Based on data from ref 12.

disorders.[20-25] Since patients with diminished insight deny the presence of certain symptoms they actually possess, lack of insight is obviously one of those subjective factors which could affect accurate diagnostic assessment of mood and psychotic disorders.

## Directions for genetic research

Turning to genetics, the ideal neurobiological hypothesis must explain two fundamental features of mood disorders: genetic vulnerability and episodic recurrence. In recent reviews of the genetic literature,[26-28] there is a consensus that findings regarding chromosomes 5, 11, and X are inconclusive; however, there are possible linkages on chromosome 18[29,30] and chromosome 21q.[31,32] In spite of these intriguing findings regarding possible single loci, most of the genetic epidemiology studies suggest a polygenic disorder.

Of relevance to genetic research is the kindling paradigm, which posits an analogy between the episodic nature of mood disorders and the phenomena of kindling and sensitization.[33] While a direct link between the physiological process of kindling and clinical recurrence has not been definitively established, the hypothesis possesses the advantage of encompassing key aspects of bipolar illness: the onset of early episodes are preceded by major stress whereas later episodes are not; the severity of untreated mood episodes worsens over time; and the interval between episodes decreases over time.[34] Now how might this have a bearing on genetic research? Compared to older animals, younger ones require a lower level of electrical or chemical stimulation to initiate and sustain limbic kindled seizures.[35] Clinical genetic data suggest 15% to 20% of children of a parent with bipolar disorder may develop the disorder. It is possible that, in the future, genetic markers with predictive validities near 80% would allow testing of the efficacy of antikindling agents in genetically vulnerable children before their first bipolar episode. Once beyond the high-risk period, one might be able to evaluate whether treatment could be withdrawn without the illness having ever expressed itself.

## Outcome

Traditionally, the outcome of patients with bipolar disorder has been reported to be intermediate between schizophrenia and nonpsychotic unipolar major depressive disorder. Recent naturalistic outcome data from several research centers suggest rather poor outcome in bipolar disorder, even when treated.[36-38] However, in evaluating the meaning of this, we must recall that tertiary care research centers include a selection bias because they treat more severely ill patients. The old adage in medicine that the longer a successful treatment is available, the more difficult it becomes to show it still works, certainly applies to lithium, where research in practice settings continues to support its effectiveness.[39] Even though early intervention may improve long-term outcome, many patients receive ineffective treatment for initial episodes, allowing the psychological and perhaps biological "scars" of episodes to linger, resulting in a more virulent illness.[33] This often involves early overuse of antidepressant agents, which may function as "mood-destabilizing" agents in bipolar disorder, an important point to which we will return later.[40]

The fact remains that there are more treatment-resistant bipolar patients today than there were two or three decades ago. Clearly, for many, the illness has changed. But why? Some of the relevant factors include the potentially destabilizing effect of chronic antidepressant treatment, cultural factors like the cocaine epidemic, and environmental factors like the increasing impact of environmental stimuli associated with modern

society. Wehr and colleagues found that when rapid-cycling bipolar patients were in a simulated environment without artificial light (10-14 hours of darkness daily), cycling improved; thus, civilization's long "unnatural" photoperiod (about 16 hours) may promote mood cycling.[41] Changes in dietary habits may also play a role. A striking negative correlation between population rates of depression and fish consumption in different countries has led to a trial of omega-3 fatty acids (rich in fish oil) in treatment-resistant bipolar patients, with striking results.[42,43] There are indications that in Western countries, especially the US, fish consumption as a proportion of our diets has declined over the past few decades, and that low omega-3 fatty acid levels are present in patients with unipolar depression.[44]

The declining age of onset and worsening course of bipolar disorder may also have, in part, a genetic explanation. Such an epidemiologic pattern ("anticipation") is known to occur in a number of neurological disorders in which triplet repeat sequences have been found to contribute to DNA instability.[45]

## Circadian rhythms and kindling

Two lines of investigation that relate directly to the unique clinical feature of recurrence in mood disorders also characterize current research. The first holds that clinical recurrence involves abnormalities in biological rhythms, especially circadian cycles, an area pioneered by Wehr and his colleagues.[46] The second posits an analogy between the episodic nature of mood disorders and electrical kindling, with behavioral sensitization to mood episodes, a hypothesis developed most extensively by Post and associates.[47]

Research on circadian rhythms suggests that abnormalities involving the suprachiasmatic nuclei (SCN) of the hypothalamus may explain many of the clinical features of recurrent mood disorders (including seasonality of episode type), perhaps through secondary effects on neurotransmitter systems. "Free-running" rhythms, cycles that are not entrained to the 24-hour day/night cycle, may desynchronize other circadian rhythms, adversely affecting mood.[46] This hypothesis has recently been supported by an animal model of a genetically fast biological clock in rats missing the tau gene, with behavioral characteristics roughly analogous to manic-depressive symptoms.[48] Eventually, genetic approaches will sharpen the research for abnormal clocks by leading to an understanding of the proteins synthesized under the direction of those genes.

The second hypothesis relevant to recurrence, as discussed previously, is the kindling paradigm. As advanced by Robert Post,[49] this theory builds on the physiological finding that in the limbic system, intermittent subthreshold electrical or chemical stimuli produce increasingly strong neuronal depolarization; such depolarization can lead to an independent permanent seizure focus, with possible behavioral effects roughly analogous to mood disorders. Thus, kindling is a process in which a highly regulated system, with multiple feedback loops, shows an escalating response to a repetitive stimulus, reaching a point where the stimulus is no longer needed for the disturbance to continue. Post drew an analogy between this phenomenon of kindling in the nervous system and the clinical observation (originally made by Kraepelin and confirmed in later more quantitative studies by Post and others) that external stress appears to activate early episodes of illness, but eventually the illness seems to take on a life of its own, with later episodes often occurring without precipitating stressors. In other words, both kindling and bipolar illness seemed to be processes of initial activation giving way, over time, to a self-driven process.

We have reviewed the clinical psychiatric literature relevant to assessing some of the predictions of the kindling hypothesis in detail elsewhere.[50] In that review, we noted that the majority of the studies support the kindling hypothesis, although with some caveats. Many were retrospective and limited to assessing hospitalized episodes of bipolar disorder. Thus, their results may not apply to milder forms of bipolar illness. In the prospective studies, nonhospitalized mood episodes were assessed, but evidence in support of kindling was not consistently attained. Some of this research suggests that kindling phenomena may characterize a subgroup of patients with bipolar disorder, perhaps with more severe illness. A recent, yet to be published, study from the National Institute of Mental Health (NIMH) Depression Collaborative research program[51] also found no evidence to support kindling-like phenomena, and instead reported that poor outcome was associated with polyphasic mood episodes, rather than monophasic mood episodes. Thus, patients whose mood episodes cycle directly between depression and mania had a worse outcome than those who experience a single episode followed by a period of euthymia. The investigators in the latter study suggest that amount of time ill is a better criterion for poor outcome than number of episodes and shortening of episode cycles, as suggested by the kindling hypothesis. There are methodological limitations to the NIMH study, as well, however; for instance, most patients were not in their early episodes of illness, which would be the period of time when the shortening of illness-free intervals between episodes, as

predicted by the kindling model, might be most evident. Thus, the clinical research on the kindling hypothesis may be interpreted as supportive of the hypothesis, albeit in a limited and not yet definitive manner.

## Patterns of mood-stabilizing treatment

Research on outcome in bipolar disorder has led to an interest in new treatments for the illness. In the last decade, anticonvulsants have assumed a well-deserved role in the treatment of bipolar disorder. Initial studies focused on lithium-resistant patients, especially rapid cycling, mixed states, and/or concurrent substance abuse. Recently, some authors have advocated anticonvulsants as treatments of first choice. Caution is in order here. The long track record of lithium provides a firm knowledge of risks and benefits. For example, lithium's impact on preventing suicide is established. A recent review of 28 studies involving over 150 suicides indicates a sixfold reduction in suicide with lithium treatment of bipolar disorder compared to no treatment.[52] The serotonergic effects of lithium implicated in the neurobiology of suicide may help explain these data.[53] A recent large prospective $2^{1}/_{2}$-year randomized study comparing lithium with carbamazepine found 9 suicide events in the carbamazepine group (5 deaths, 4 severe attempts) versus none for the lithium group ($P<0.02$).[54] Meanwhile, a 1-year multisite study of divalproex prophylaxis could not establish a significant advantage over placebo.[55] While this negative finding may stem from inadequate statistical power since severely ill patients were excluded, nonetheless, the lack of a robust prophylactic effect in those patients studied suggests caution. In an earlier multisite study comparing the acute antimanic effects of divalproex, lithium, and placebo, those patients with a history of prior response to lithium had a robust antimanic response to its readminstration, but the divalproex response in this group was only 27%. On the other hand, those with a prior history of nonresponse to lithium showed a relatively high rate of response to the anticonvulsant, suggesting that there may be two substantially separable antimanic response patterns. Since antimanic response may predict prophylactic efficacy,[39,56-58] this highlights the danger of discontinuing lithium treatment in responders to it. Also, lithium discontinuation (especially when abrupt) promotes rapid relapse.[59,60] The possibility of lithium withdrawal–induced treatment refractoriness has also been raised,[61] though not settled.[62]

## The antidepressant problem

Not surprisingly, patients with bipolar disorder often are more aware of depression and its concomitant symptoms than they are of mood elevation. Hence, even in the midst of an episode of mood elevation, they may present requesting antidepressant treatment and often refuse mood stabilizers. Regardless of whether these patients are simply less concerned about the consequences of mood elevation or are relatively insensitive in perceiving it, the demand for antidepressant treatment presents a clinical dilemma. Considerable evidence suggests a relationship between chronic antidepressant treatment, especially without concurrent mood-stabilizing treatment, and development of treatment resistance. Goodwin and Jamison have reviewed this matter and marshaled much of the relevant data.[34] Briefly, in three double-blind outcome studies, the rate of manic episodes in patients with bipolar disorder treated with antidepressants and lithium is roughly twice the rate of those treated with lithium alone.[56,63,64] In two studies of patients with rapid-cycling, antidepressants were thought to be the likely causes of rapid-cycling in 26% to 35% of cases (n=85).[65,66] Using mood charting, Wehr and Goodwin[67] also documented increased frequency of affective cycles in patients treated with desipramine (and lithium) instead of lithium alone. The risks of antidepressant use documented in these studies are summarized in *Table I.*

The absence of systematic or objective measures for cycling may account for the general underrecognition of these phenomena. Simple reliance on the patient's subjective self-report often is insufficient. The limitations of self-report can be decreased by systematically collecting information from other sources, such as mood charting and family reports. In a recent examination of diagnosis and treatment practices,[9] we found that one third of bipolar patients admitted to the hospital were taking antidepressant agents, whereas all but 4% were able to be discharged in 1 to 2 weeks without them (even 50% of acutely depressed bipolar patients improved at least mildly without antidepressant agents). It seems that the clinical importance of minimizing acute antidepressant

| Risks with antidepressants |
|---|
| Acute mania |
| Rapid-cycling |
| Treatment resistance to mood stabilizers |

**Table I.** The antidepressant problem.

treatment and emphasizing aggressive mood-stabilizing prophylaxis has yet to be fully appreciated in clinical practice. If antidepressants are used, bupropion[68] or paroxetine[69] may be the least risky since they are the only two new antidepressants that have been shown, in double-blind randomized studies of add-on therapy with lithium, to have a lower risk of precipitating mania than tricyclic antidepressants. Nonetheless, all antidepressants appear to have longer-term risks of promoting rapid cycling.

## Neurobiological research in bipolar disorders: the state of the art

Clinical psychopharmacology is, of course, dependent on advances in neurobiology. Here, an evolution has occurred. Early studies from the 1960s and 1970s were influential in developing neurobiological hypotheses based on functioning of central nervous system (CNS) monoamine systems, as suggested by the efficacy of antidepressant and mood-stabilizing agents and then testing those hypotheses through innovative approaches to the direct assessment of amine metabolism in patients. These studies emphasized possible excess or deficiency states of monoamines such as norepinephrine, dopamine, or serotonin.[70,71] Later work centered on interactions among monoamine systems, indicating that even "selective" new-generation psychotropic agents have multiple effects within the brain based on extensive neuronal interconnectivity among monoaminergic tracts within limbic regions. Starting in the 1970s, a number of investigators began to emphasize the importance of moving beyond excess or deficiency states to an understanding of regulatory systems.[72,73] More recently, the evaluation of regulatory function in relation to affective disturbances has been accelerated by rapid progress in the delineation of specific neuronal tracts and their interconnections, especially as modeled by neural network paradigms.[74,75]

Another line of advance in the neurobiological investigation of bipolar disorder has been the evolution from synaptic neurotransmitter–based hypotheses as discussed above to postsynaptic second messenger-based hypotheses. Manji[76] has suggested a central role for G-proteins in the mechanism of action of lithium, a role which may be more important pathophysiologically than lithium's synaptic effects. If this is true, similar second messenger postsynaptic mechanisms may remain to be discovered as possibly underlying sources of action of other mood-stabilizing agents, such as valproate and carbamazepine, as well as some antidepressants. Particularly relevant to bipolar disorder, second messenger mechanisms may explain the unique mood-stabilizing effects of lithium and other agents that produce psychomotor activation and mood elevation in the depressed state, reduce them in the manic state, and have little effect on the euthymic state. For instance, Berridge and colleagues[77] hypothesized that lithium selectively inhibits the second messenger phosphatidylinositol in neuronal pathways that are overactive; this would suppress an excessively excited system, but exert no effect on a normally functioning pathway. Such second messenger systems generally are linked initially to G-proteins that translate synaptic neurotransmission into intracellular changes, such as with phosphatidylinositol. Medications developed on the basis of these specific effects on different G-proteins are in process of early clinical evaluation and may prove to be more pharmacologically specific in bipolar disorder than current treatments. In this regard, the recent preliminary finding that high doses of omega-3 fatty acids may have mood-stabilizing properties in bipolar disorder is of considerable interest, given the role of these essential fatty acids in postsynaptic signal transduction.[78] Further work on postsynaptic mechanisms has involved other aspects of cellular communication linked to G-protein function, particularly the activity of the enzyme protein kinase C. We have summarized much of this research in *Table II (see next page)*.

Eventually, understanding of such intracellular mechanisms may lead to explication of alterations in gene expression that may be involved in the pathogenesis or treatment of mood disorder.

Advances in neuroimaging represent another exciting area of progress in neurobiological research. Mood disorders still lag behind schizophrenia in being a focus of such work, and future neuroimaging research should focus more on the need for such data in mood disorders. As Meltzer[79] has noted, much of the available neuroimaging research on mood disorders has not demonstrated clear differences from findings in schizophrenia, which some have taken to support the unitary psychosis diagnostic model. However, the relative paucity of work in mood disorders raises the likelihood of type II error in the interpretation of available small data sets due to lack of statistical power to find existent differences. Functional neuroimaging in particular may demonstrate more subtle pathophysiological differences that may have eluded structural brain imaging such as computed tomography or magnetic resonance imaging. Again, the importance of state vs trait differences needs to be reemphasized, since it is more relevant to recurrent conditions such as mood disorders than to chronic conditions such as schizophrenia.

| |
|---|
| **G-proteins** |
| • Stimulatory G-protein levels may be elevated compared to controls in patients with bipolar disorder; whether these differences are state- or trait-dependent is unclear |
| • Lithium may decrease activity of certain pathways by inhibiting certain stimulatory G-proteins (Gs) |
| • Lithium may increase activity of certain pathways by inhibiting certain inhibitory G-proteins (Gi) |
| **Other second messengers** |
| • Phosphatidylinositol (PI): lithium or valproate reduces PI activity and depletes intracellular inositol |
| • Protein kinase C (PKC): chronic lithium or valproate use impairs PKC activity and reduces PKC levels |
| • Myristoylated alanine-rich C kinase substrate (MARCKS): chronic lithium use impairs MARCKS activity |
| • Intracellular calcium: increased intraneuronal levels in patients with bipolar disorder. Reduction by calcium channel blockers may produce antimanic efficacy. Augmentation by lithium may produce antidepressant efficacy |
| **Genetic expression** |
| • Lithium augments expression of certain parts of the *c-fos* gene, mediated mainly by PI and PKC |

**Table II.** Findings regarding second messenger systems in bipolar disorder.

## Integrating biological and psychosocial aspects of bipolar disorder

While research in neurobiology is central to understanding bipolar disorder, psychosocial research is also vital. In the future, we hope that theories regarding mood disorders suffer less from the reductionistic effects of Cartesian dualism than in the past. Given the emerging realization that mind and brain are not different entities belonging to different realms of experience, the distinction between the biological and the psychosocial aspects of illness begins to break down. Advances in biological research itself support this approach. New developments in neuroscience are beginning to show that even subtle changes in the environment (especially early in life) can result in long-lasting changes in the brain. These advances are based on new insights into the plasticity of the CNS, with elegant demonstrations of often-specific environmental influences on specific neurobiological processes, including gene expression. Thus, for example, in the study of stress effects, the field has moved rapidly beyond immediate, often sort-term biological responses (eg, hypothalamic-pituitary-adrenal axis activation) to demonstrations of environmental manipulations producing long-lasting, even permanent changes. These changes have been shown to operate through receptor-coupled intracellular signal transduction pathways regulating gene expression that, in turn, alters the synthesis of specific proteins and cell components. Kandel[80] has suggested that a mechanism of action for psychotherapy may involve these kinds of alterations in synaptic structure and function. If this is true, then medication treatment and psychotherapy may be acting through a similar final common pathway—the brain. This view is supported by recent work in obsessive-compulsive disorder, where behavior therapy was shown to produce similar changes in positron emission tomography neuroimaging as did medication treatment, leading Baer[81] to suggest that behavior therapy may be a form of "endogenous serotonin therapy." More work will be needed in this fruitful field of translating psychotherapeutic treatment into alterations in brain structure and function.

Once the brain is understood to be a final common pathway for both medication and psychotherapeutic treatments, then the importance of balancing biological and psychosocial approaches becomes more understandable. The brain mediates both treatment approaches. It may be, then, that a mood disorder may have a largely biological origin, and yet be responsive to psychotherapy. Conversely, a mood disorder may be largely psychosocial in origin, and yet respond to medication treatment. It is an elementary error of logic to reason from conclusion to premises; one must always work the other way around. While the etiology of a certain condition may be psychological, its pathogenesis may be biological and hence amenable to biological interventions (and, at least theoretically, vice versa). Hence, while the efficacy of pharmacological or psychotherapeutic treatments may give us clues about where we need to look in the search for the etiologies of mood disorders, in themselves the fact that these treatments work does not establish any specific etiology. Advances in neurobiology, in particular, should complement, rather than curtail, psychosocial research and psychotherapeutic practice.

This perspective is supported by some recent psychosocial research in bipolar disorder. Since many outcome studies have found marked impairment in social and occupational functioning in bipolar disorder despite some symptomatic improvement pharmacologically, one might conclude that psychotherapeutic interventions are able to improve social and occupational functioning. Recent data support this hypothesis, which experienced clinicians already know: combined psychosocial/pharmacological strategies are more effective than medication alone, especially in improving function, reducing relapse, and preventing hospitalization. [82,83]

## Conclusions

The state of the art in the diagnosis and treatment of bipolar disorder is both heartening and challenging. We have come a long way and appear to be headed in the right direction. However, we face a number of challenges, which, with effort and foresight, we should be able to meet. First, we need to


### Trastorno bipolar

*La singular combinación de tres características en los trastornos bipolares - clara diátesis genética, características clínicas distintivas y la rápida disponibilidad de un tratamiento eficaz (el litio) - explica el lugar especial que ocupan en la historia de la psiquiatría y su contribución al crecimiento explosivo de las neurociencias. El presente artículo aborda las mejores perspectivas en el trastorno bipolar desde diferentes ángulos: 1) genético (enlaces posibles en los cromosomas 18 y 21q, hipótesis poligénica, investigaciones sobre marcadores biológicos); 2) diagnóstico (nuevo enfoque sobre los aspectos subjetivos del trastorno bipolar para compensar la tendencia actual a subdiagnosticarlo debido a un exceso de confianza en las entrevistas estandardizadas y las escalas de evaluación); 3) resultados (aumento de las formas resistentes al tratamiento lo que indica un cambio en la historia natural del trastorno bipolar); 4) patofisiología (investigación del papel de los ciclos circadianos biológicos y de las hipótesis que explican las recurrencias); 5) tratamiento (aparición de los anticonvulsivos, papel supuesto del tratamiento antidepresivo de larga duración en el desarrollo de una resistencia al tratamiento); 6) neurobiología (evaluación de la función reguladora en los trastronos afectivos, papel del mecanismo del segundo mensajero, avances en las neuroimágenes funcionales); por último, 7) investigación psicosocial (revisión de las antiguas teorías dualistas para comprender la mente y el cerebro como entidad enfatizando, así, la importancia del enfoque equilibrado: psicofarmacológico y psicoterapéutico). El progreso futuro en la comprensión y el tratamiento del trastorno bipolar se apoyará en la exitosa integración de los ejes de investigación biológico y psicosocial.*

### Trouble bipolaire

*L'association unique des trois caractéristiques du trouble bipolaire - terrain génétique manifeste, signes cliniques typiques, découverte précoce d'un traitement efficace (lithium) - explique la place particulière qu'il tient au sein de l'histoire de la psychiatrie et sa contribution à la croissance explosive actuelle des neurosciences. Cet article donne un aperçu de l'état de nos connaissances sur le trouble bipolaire à partir des points de vue : 1) de la génétique (liaisons possibles sur les chromosomes 18 et 21q, hypothèses polygéniques, recherche de marqueurs génétiques); 2) du diagnostic (éclairage nouveau sur les aspects subjectifs du trouble bipolaire pour compenser la tendance actuelle à sous-diagnostiquer due à une confiance excessive dans les entretiens standardisés et les échelles d'évaluation; 3) du devenir (augmentation des formes résistantes au traitement témoignant d'un changement dans l'histoire naturelle du trouble bipolaire); 4) de la physiopathologie (recherche sur les rythmes biologiques circadiens et l'hypothèse d'embrasement pour expliquer les rechutes); 5) du traitement (émergence des anticonvulsivants, suggestion d'un rôle joué par le traitement antidépresseur chronique dans le développement des résistances au traitement); 6) de la neurobiologie (évaluation de la fonction de régulation en relation avec des troubles affectifs, rôle des méca-nismes de seconds messagers post-synaptiques, progrès en neuro-imagerie fonctionnelle); et 7) de la recherche sociopsychologique (s'éloigner des théories du passé trop dualistes pour comprendre l'esprit et le cerveau en tant qu'une seule entité, soulignant ainsi l'importance de l'équilibre entre les approches psychopharmacologiques et psychothérapeutiques). Les progrès ultérieurs dans la compréhension et le traitement du trouble bipolaire dépendront de l'intégration réussie des voies d'investigation biologiques et sociopsychologiques.*

avoid an historical tendency in psychiatry towards reductionism, which led to a swing away from biological work for much of this century. Yet, as much as nonbiological approaches, biological psychiatry carries a risk of going too far with untested assumptions. We must promote further progress in the burgeoning field of neurobiological research and inform it clinically with an understanding of important features of psychiatric illnesses such as recurrence and genetic susceptibility. We should recall the two-way interaction between clinical research and laboratory investigation, without ignoring either side of this important paradigm for progress. And we need to integrate biological and psychosocial lines of investigation much better than in the past. Ultimately, these efforts all pay off at the clinic and at the bedside, where we may assist individuals suffering from bipolar illness to recover and return to their lives free of its ravages. ❑

## REFERENCES


**1.** van Praag HM. *"Make-Believes" in Psychiatry Or The Perils of Progress.* New York, NY: Brunner/Mazel; 1993.
**2.** Johnson FN. *The History of Lithium Therapy*. London, UK: Macmillan; 1984.
**3.** Robins E, Guze SB. Establishment of diagnostic validity in psychiatric illness: its application to schizophrenia. *Am J Psychiatry.* 1970;126:983-987.
**4.** Kendell RE, Brockington IF. The identification of disease entities and the relationship between schizophrenic and affective psychoses. *Br J Psychiatry.* 1980;137:324-331.
**5.** Crow TJ. The continuum of psychosis and its implication for the structure of the gene. *Br J Psychiatry.* 1986;149:419-429.
**6.** Cloninger CR, Martin RL, Guze SB, Clayton PJ. Diagnosis and prognosis in schizophrenia. *Arch Gen Psychiatry.* 1985;42:15-25.
**7.** Tsuang MT, Winokur G, Crowe RR. Morbidity risks of schizophrenia and affective disorders among first degree relatives of patients with schizophrenia, mania, depression, and surgical conditions. *Br J Psychiatry*. 1980;137:497-504.
**8.** Pope HG Jr, Lipinski JF. Diagnosis in schizophrenia and manic-depressive illness. *Arch Gen Psychiatry.* 1978;35:811-828.
**9.** Ghaemi SN, Sachs GS, Chiou AM, Pandurangi AK, Goodwin FK. Differential diagnosis of bipolar disorder and the use of antidepressants: is bipolar disorder underdiagnosed? Are antidepressants overutilized? *American College of Neuropsychopharmacology.* San Juan, Puerto Rico; 1996. Abstract.
**10.** Havens L. *Making Contact: Uses of Language in Psychotherapy.* Cambridge, Mass: Harvard University Press; 1986.
**11.** Sullivan HS. *The Psychiatric Interview.* New York, NY: Norton; 1954.
**12.** Anthony JC, Folstein M, Romanoski AJ et al. Comparison of lay diagnostic interview schedule and a standardized psychiatric diagnosis. Experience in Eastern Baltimore. *Arch Gen Psychiatry.* 1985;42:667-675.
**13.** Regier DA, Kaelber CT. The epidemiologic catchment area (ECA) program: studying the prevalence and incidence of psychopathology. In: Tsuang MT, Tohen M, Zahner GEP, eds. *Textbook in Psychiatric Epidemiology.* New York, NY: John Wiley; 1995:133-157.
**14.** Kessler RC, McGonagle KA, Zhao S. Lifetime and 12-month prevalence of DSM-III-R psychiatric disorders in the United States. *Arch Gen Psychiatry.* 1994;51:8-19.
**15.** Kendler KS, Gallagher TJ, Abelson JM, Kessler RC. Lifetime prevalence, demographic risk factors, and diagnostic validity of nonaffective psychosis as assessed in a US community sample: the national comorbidity survey. *Arch Gen Psychiatry.* 1996;53:1022-1031.
**16.** McEvoy JP, Aland J Jr, Wilson WH, Guy W, Hawkins L. Measuring chronic schizophrenic patients attitudes toward their illness and treatment. *Hosp Community Psychiatry.* 1981;32:856-858.
**17.** Amador XF, Strauss DH, Yale SA, Gorman JM. Awareness of illness in schizophrenia. *Schizophr Bull.* 1991;17:113-132.
**18.** David AS. Insight and psychosis. *Br J Psychiatry.* 1990;156:798-808.
**19.** Markova IS, Berrios GE. The assessment of insight in clinical psychiatry: a new scale. *Acta Psychiatr Scand.* 1992;86:159-164.
**20.** McEvoy JP, Apperson LJ, Appelbaum PS, et al. Insight in schizophrenia. Its relationship to acute psychopathology. *J Nerv Ment Dis* 1989;177:43-47.
**21.** Amador XA, Flaum M, Andreasen NC, et al. Awareness of illness in schizophrenia and schizoaffective and mood disorders. *Arch Gen Psychiatry.* 1994;51:826-836.
**22.** David A, Buchanan A, Reed A, Almeida O. The assessment of insight in psychosis. *Br J Psychiatry.* 1992;161:599-602.
**23.** Michalakeas A, Skoutas C, Charalambous A, et al. Insight in schizophrenia and mood disorders and its relation to psychopathology. *Acta Psychiatr Scand.* 1994;90:46-49.
**24.** Cuesta MJ, Peralta V. Lack of insight in schizophrenia. *Schizophr Bull.* 1994;20:359-366.
**25.** Ghaemi SN, Stoll AL, Pope HG. Lack of insight in bipolar disorder. *J Nerv Ment Dis.* 1995;183:464-467.
**26.** DePaulo JR, McMahon FJ. Recent developments in the genetics of bipolar disorder. *Cold Spring Harbor Symposia on Quantitative Biology.* Cold Spring Harbor, NY; 1996;61:783-789.
**27.** Berrettini W. Diagnostic and genetic issues of depression and bipolar illness. *Pharmacotherapy.* 1995;15(6 pt 2):69S-75S.
**28.** Kelsoe JR. The genetics of bipolar disorder. *Psychiatr Ann.* 1997;27:285-292.
**29.** Berretini WH, Ferraro TN, Goldin LR, et al. A linkage study of bipolar illness. *Arch Gen Psychiatry.* 1997;54:27-35.
**30.** Stine OC, Xu J, McMahon FJ, et al. Evidence for linkage of bipolar disorder to chromosome 18 with a parent-of-origin effect. *Am J Hum Genet.* 1995;57:1384-1394.
**31.** Straub RE, Lehner T, Luo Y, et al. A possible vulnerability locus for bipolar affective disorder on chromosome 21q22.3. *Nat Genet.* 1994;8:291.
**32.** Detera-Wadleigh SD, Badner JA, Goldin LR, et al. Affected-sib-pair analyses reveal support of prior evidence for a susceptibility locus for bipolar disorder on 21q. *Am J Hum Genet.* 1996;58:1279.
**33.** Post RM, Weiss SRB. The neurobiology of treatment-resistant mood disorders. In: Bloom FE, Kupfer DJ, eds. *Psychopharmacology: The Fourth Generation of Progress.* New York, NY: Raven Press; 1995:1155-1170.
**34.** Goodwin FK, Jamison KR. *Manic Depressive Illness.* New York, NY: Oxford University Press; 1990.
**35.** Fanelli RJ, McNamara JO. Effects of age on kindling and kindled seizure-induced increase of benzodiazepine receptor binding. *Brain Res.* 1986;362:17-22.
**36.** Harrow M, Goldberg JF, Grossman LS, Meltzer HY. Outcome in manic disorders. *Arch Gen Psychiatry.* 1990;47:665-671.
**37.** Tohen M, Waternaux CM, Tsuang M. Outcome in mania: a 4-year prospective follow-up of 75 patients utilizing survival analysis. *Arch Gen Psychiatry.* 1990;47:1106-1111.
**38.** Sachs GS, Lafer B, Truman CJ, Noeth M, Thibault AB. Lithium monotherapy: miracle, myth and misunderstanding. *Psychiatr Ann.* 1994;24:299-306.
**39.** Page C, Benaim S, Lappin F. A long-term retrospective follow-up study of patients treated with prophylactic lithium carbonate. *Br J Psychiatry.* 1987;150:175-179.
**40.** Wehr TA, Goodwin FK. Can antidepressants cause mania and worsen the course of affective illness? *Am J Psychiatry.* 1987;144:1403-1411.
**41.** Wehr TA, Turner EH, Shimada JM, Clark CH, Barker C, Leibenluft E. Treatment of a rapidly-cycling bipolar patient by using extended bedrest and darkness to stabilize the timing and duration of sleep. *Biol Psychiatry.* 1998;43:822-828.
**42.** Hibbeln JR, Salem N. Dietary polyunsaturated fatty acids and depression: when cholesterol does not satisfy. *Am J Clin Nutr.* 1995;62:1-9.
**43.** Hibbeln J, Umhau J, George D, Salem NJ. Do plasma polyunsaturates predict hostility and depression? *World Rev Nutr Diet.* 1997;82:175-186.

**44.** Peet M, Murphy B, Shay J, Horrobin D. Depletion of omega-3 fatty acid levels in red blood cell membranes of depressive patients. *Biol Psychiatry.* 1998;43:315-319.
**45.** McInnis MG, McMahon FJ, Chase GA, Simpson SG, Ross CA, DePaulo JR. Anticipation in bipolar affective disorder. *Am J Hum Genet.* 1993;53:385-390.
**46.** Wehr TA, Goodwin FK. Biological rhythms in manic-depressive illness. In: Wehr TA, Goodwin FK, eds. *Circadian Rhythms in Psychiatry.* Pacific Grove, Calif: Boxwood; 1983:129-184.
**47.** Post RM, Putnam F, Contel NR, Goldman B. Electroconvulsive seizures inhibit amygdala kindling: implications for mechanisms of action in affective illness. *Epilepsia.* 1984;25:234-239.
**48.** Weaver D. The suprachiasmatic nucleus: a 25-year retrospective. *J Biol Rhythms.* 1998;13:100-112.
**49.** Post RM. The transduction of psychosocial stress into the neurobiology of recurrent affective illness. *Am J Psychiatry.* 1992;149:999-1010.
**50.** Ghaemi SN, Boiman EE, Goodwin FK. Kindling and second messengers: an approach to the neurobiology of recurrence in bipolar disorder. *Biol Psychiatry* 1998. In press.
**51.** Turvey C, Coryell W, Solomon D, Leon A, Endicott J, Akiskal H. Long-term prognosis of bipolar I disorder. *Annual Meeting of the Psychiatric Research Society.* Park City, Utah; 1998.
**52.** Tondo L, Jamison K, Baldessarini R. Effect of lithium maintenance on suicidal behavior in major mood disorders. In: Stoff D, Mann J, eds. *The Neurobiology of Suicide: From the Bench to the Clinic.* Vol 836. New York, NY: The New York Academy of Sciences; 1997:339-351.
**53.** Bunney W, Garland-Bunney B. Mechanisms of action of lithium in affective illness: basic and clinical implications. In: Meltzer H, ed. *Psychopharmacology: The Third Generation of Progress.* New York, NY: Raven Press; 1987:553-565.
**54.** Theis-Flechtner K, Müller-Oerlinghausen B, Seibert W, Walther A, Greil W. Effect of prophylactic treatment on suicide risk in patients with major affective disorders: data from a prospective randomized trial. *Pharmacopsychiatry.* 1996;29:103-107.
**55.** Bowden CL. Maintenance treatments for bipolar disorder. *37th Annual Meeting of the New Clinical Drug Evaluation Unit.* Boca Raton, Fla; 1997.
**56.** Prien RF, Klett CJ, Caffey EM. Lithium prophylaxis in recurrent affective illness. *Am J Psychiatry.* 1974;131:198-203.
**57.** Abou-Saleh MT, Coppen A. Who responds to prophylactic lithium? *J Affect Disord.* 1986;10:115-125.
**58.** Dunner D, Fieve R. Clinical factors in lithium carbonate prophylaxis failure. *Arch Gen Psychiatry.* 1974;30:229-233.
**59.** Suppes T, Baldessarini RJ, Faedda GL, Tohen M. Risk of reoccurrence following discontinuation of lithium treatment in bipolar disorder. *Arch Gen Psychiatry.* 1991;48:1082-1088.
**60.** Baldessarini RJ, Tondo L, Floris G, Rudas N. Reduced morbidity after gradual discontinuation of lithium treatment for bipolar I and II disorders: a replication study. *Am J Psychiatry.* 1997;154:551-553.
**61.** Post RM, Leverich GS, Altshuler LL, Mikalauskas K. Lithium discontinuation-induced refractoriness: preliminary observations. *Am J Psychiatry.* 1992;149:1727-1729.
**62.** Tondo L, Baldessarini RJ, Floris G, Rudas N. Effectiveness of restarting lithium treatment after its discontinuation in bipolar I and bipolar II disorders. *Am J Psychiatry.* 1997;154:548-550.
**63.** Prien R, Kupfer D, Mansky P, et al. Drug therapy in the prevention of recurrences in unipolar and bipolar affective disorders. *Arch Gen Psychiatry.* 1984;41:1096-1104.
**64.** Quitkin FM, Kane J, Rifkin A, Ramos-Lorenzi JR, Nayak DV. Prophylactic lithium carbonate with and without imipramine for bipolar 1 patients. *Arch Gen Psychiatry.* 1981;38:902-907.
**65.** Goodwin GM. Recurrence of mania after lithium withdrawal: implications for the use of lithium in the treatment of bipolar affective disorder. *Br J Psychiatry.* 1994;164:149-152.
**66.** Kukopulos A, Reginaldi P, Laddomada G, Floris G, Serra G, Tondo L. Course of the manic-depressive cycle and changes caused by treatments. *Pharmacopsychiatry.* 1980;13:156-167.
**67.** Wehr TA, Goodwin FK. Rapid cycling in manic-depressives induced by tricyclic antidepressants. *Arch Gen Psychiatry.* 1979;36:555-559.
**68.** Sachs GS, Lafer B, Stoll AL, et al. A double-blind trial of bupropion versus desipramine for bipolar depression. *J Clin Psychiatry.* 1994;55:391-393.
**69.** Young ML, Pitts CD, Oakes R, Gergel IP. A double-blind placebo-controlled trial comparing the effect of paroxetine and imipramine in the treatment of bipolar depression. *2nd International Conference on Bipolar Disorder.* Pittsburgh, Pa; 1997.
**70.** Schildkraut JJ. The catecholamine hypothesis of affective disorders: a review of supporting evidence. *Am J Psychiatry.* 1965;122:509-522.
**71.** Bunney WE Jr, Davis J. Norepinephrine in depressive reactions. *Arch Gen Psychiatry.* 1965;13:483-494.
**72.** Goodwin FK, Bunney WE Jr. Depressions following reserpine: a reevaluation. *Semin Psychiatry.* 1971;3:435-448.
**73.** Mandell AJ. Asymmetry and mood-emergent properties of serotonin regulation. *Arch Gen Psychiatry.* 1979;36:909-916.
**74.** Hyman SE, Gollub RL. More serotonin: not as simple as it seems. *Harv Rev Psychiatry*. 1994;2:222-224.
**75.** Siever LJ, Davis KL. Overview: toward a dysregulation hypothesis of depression. *Am J Psychiatry.* 1985;142:1017-1031.
**76.** Manji HK. G-proteins: implications for psychiatry. *Am J Psychiatry.* 1992;149:746-760.
**77.** Berridge M, Downes CP, Hanley MR. Neural and developmental actions of lithium: a unifying hypothesis. *Cell.* 1989;59:411-419.
**78.** Nunez E. Fatty acids involved in signal cross-talk between cell membrane and nucleus. *Prostaglandins Leukot Essent Fatty Acids.* 1997;57:429-434.
**79.** Melter HY. Schizoaffective disorder: is the news of its nonexistence premature? *Schizophr Bull.* 1984;10:11-29.
**80.** Kandel ER. Psychotherapy and the single synapse. *N Engl J Med.* 1979;301:1028-1037.
**81.** Baer L. Behavior therapy: endogenous serotonin therapy? *J Clin Psychiatry.* 1996;57(suppl 6):33-35.
**82.** Miklowitz DJ, Goldstein MJ, Nuechterlein KH. Expressed emotion, affective style, lithium compliance, and relapse in recent onset mania. *Psychopharmacol Bull.* 1986;22:628-632.
**83.** Milkowitz DJ. Psychotherapy in combination with drug treatment for bipolar disorder. *J Clin Psychopharmacol.* 1996;16(suppl 1):56S-66S.