REVIEW ARTICLE

MEDICAL PROGRESS

Bipolar Disorder

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Bipolar disorder is one of the most distinct syndromes in psychiatry and has been described in numerous cultures over the course of history.[1] The unique hallmark of the illness is mania. Mania is, in many ways, the opposite of depression. It is characterized by elevated mood or euphoria, overactivity with a lack of need for sleep, and an increased optimism that usually becomes so extreme that the patient's judgment is impaired. For example, a person with mania may decide to purchase 500 television sets if he or she believes that their price will go up. Drives such as sexual desire are also enhanced; manic patients are disinhibited in their speech about sexual matters, joking or talking about subjects not normally allowed in their culture. Manic patients are sometimes disinhibited in their sexual actions as well, and they may endanger their marriage or relationship as a result. A key point is that manic behavior is distinct from a patient's usual personality, but its onset may be gradual with weeks or months passing before the syndrome becomes full-blown. In the absence of effective treatment, a manic episode, although ultimately self-limited, could last months or years.[2] Before effective treatment was available, even after a long manic episode, patients were known to recover to a state closely approximating, if not identical with, their personality before the illness developed.[3]

The depression that alternates with manic episodes (bipolar depression) is characterized by more familiar symptoms (Table 1). A single manic episode is sufficient for the diagnosis of bipolar illness, as long as the manic symptoms are not due to a general medical condition such as amphetamine abuse or pheochromocytoma.[4] Some patients may have one manic episode at a young age and frequent depressive episodes thereafter, others may have alternating episodes of mania and depression on a yearly basis, and still others may have a manic episode every five years but never have a depressive episode.

DEFINITIONS

Mania can be of varying severity. Mild episodes without psychotic symptoms and without symptoms of being dangerous to oneself or to others are called hypomania.[5] Hypomanic episodes can occur in patients with diagnosed bipolar illness, but they can also occur in patients with a history only of depression. The syndrome of major depressive episodes and hypomanic episodes has been called bipolar II disorder, to distinguish it from the full-blown bipolar illness called bipolar I disorder. However, the reliability of the diagnosis of bipolar II disorder is lower than for bipolar I disorder, and drug response and family history do not convincingly indicate that bipolar II is truly a milder version of the disorder.[5]

Bipolar illness (classically defined bipolar I disorder) affects approximately 1 percent of the population worldwide.[6] Bipolar II disorder is reported to be much more prevalent, and a spectrum of bipolar disorder has been described that includes states of chronic mild hypomania.[7] However, the use of the concept that bipolar illness covers a wide

Table 1. Features of Bipolar Disorder.

Feature	Mania	Hypomania	Depression
Severity of disorder	Severity requires hospitalization in most cases, because of major impairment in occupational and social functioning	Does not require hospitalization; unusual demeanor and uncharacteristic behavior noticeable by others, for at least several days	Depressed mood or reduced interest or pleasure in activities, for at least 2 wk; behavior and demeanor different from usual personality, causing noticeable impairment in social, occupational, and other areas of functioning
Symptoms	Euphoria or irritable mood; decreased need for sleep; talkativeness; racing thoughts; increased sexual activity and aggressive activity; increased motor activity or agitation; poor judgment	Same as in mania	Reduced appetite and weight loss; insomnia (especially early-morning awakening); fatigue; feelings of worthlessness; poor concentration; suicidal thoughts; decreased interest in sexual activity and in other pleasurable activities

spectrum may result in labeling patients as having this disorder and may result in clinicians' overprescribing drugs and framing psychosocial issues as medical.

Patients who have four or more episodes of mania or depression per year are considered to be "rapid cyclers," and rapid cycling is difficult to treat. Although some experts have advocated specific pharmacologic treatment, a recent large, controlled study showed that valproate was not superior to lithium in the treatment of these patients.[8] Furthermore, there are few life-course studies, and many clinicians have observed that in some patients a period of a few years of rapid cycling occurs, with a later transition to a period of less frequent episodes, and vice versa.[9]

The lifetime incidence of about 1 percent for bipolar disorder contrasts by an order of magnitude with estimates of the prevalence of unipolar depression, which is far more common in the general population. However, bipolar disorder, especially in the manic phase, is so destructive to the patient's ability to work and to the function of the family that it constitutes a substantial public health problem even in comparison with the more common unipolar depression.[10]

For women with bipolar disorder, the postpartum period is a time of considerable risk, and this fact should be discussed when counseling female patients about the risk of pregnancy. Bipolar illness may also have its onset post partum, and manic symptoms that appear in the weeks after delivery do not have the good prognosis characteristic of mild depressive postpartum symptoms. Alcohol abuse and drug abuse frequently complicate the treatment of patients with bipolar disorder and the clinical course of the disease, because patients in the depressive phase may use alcohol or drugs as self-medication and patients in the manic phase may crave them as part of the arousal characteristic of this phase. The extent of substance abuse in patients with bipolar disorder varies greatly according to culture, country of residence, and socioeconomic class.

Figure 1 presents a life chart of a patient with bipolar disorder and shows the episodes of mania and depression that affected the patient's life, ruining several potential careers and leading to three divorces. In the healthy intervals, the patient clearly regretted some of his behavior during the periods of depression and mania; when well, he saw such behavior as not part of himself.

Many famous musicians, writers, and leaders of society have had bipolar disorder.[11] Many of these people — and some of their physicians — have been concerned that the pharmacologic treatment of their mood swings might reduce their creativity. However, there is considerable evidence that people with bipolar disorder are more creative when effectively treated than when they are not treated. Only the early phases of mania appear to contribute to creativity, whereas full-blown mania usually becomes destructive to creativity and productivity.[12]

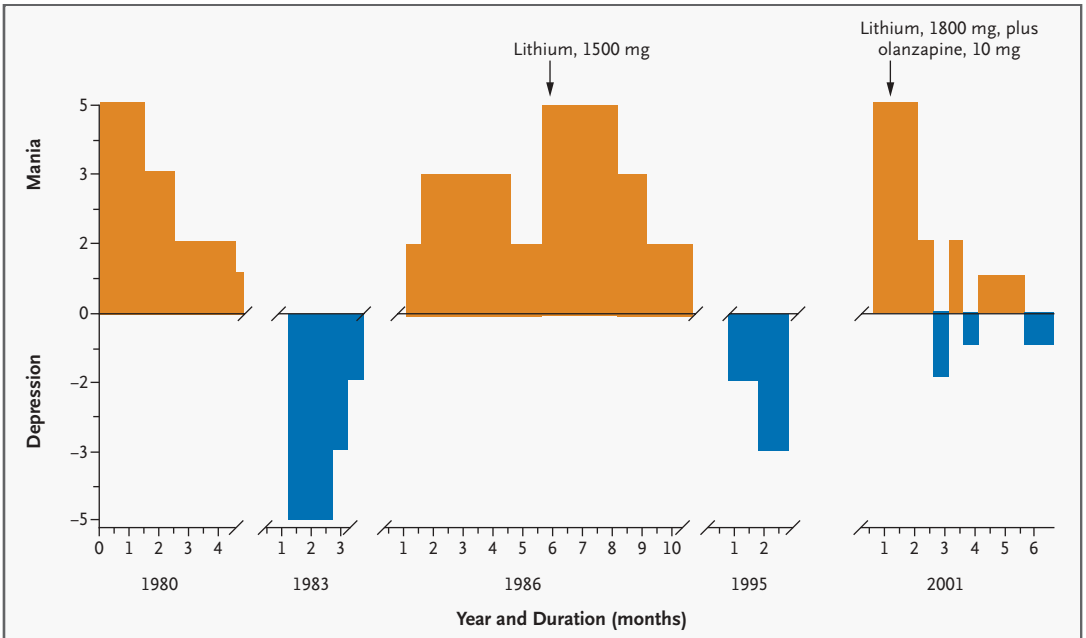

Figure 1. Life Chart of a Patient with Bipolar Illness.

The patient was a 43-year-old man who had a first episode of mania at the age of 23 and a first episode of depression at the age of 27. Orange denotes mania, and blue depression. Positive scores indicate mania and negative scores depression, with higher scores indicating a greater severity of illness and zero indicating no illness.

GENETICS

About 50 percent of patients with bipolar illness have a family history of the disorder, and in some families, known as multiplex families, there are many members with the disease across several generations. Studies of twins suggest that the concordance for bipolar illness is between 40 percent and 80 percent in monozygotic twins and is lower (10 to 20 percent) in dizygotic twins, a difference that suggests a genetic component to the disorder.[13] There is no mendelian pattern, however, and statistical analysis suggests polygenic inheritance.

The advent of molecular genetics opened a new era in genetic studies of bipolar disorder. DNA markers have been sought throughout the genome in large pedigrees in which many family members have the illness and, with the use of the transmission disequilibrium test, in patients with bipolar disorder and their parents. Linkage studies have identified markers, which have been replicated in more than one study, particularly on chromosomes 18 and 22.[14] However, no single locus has been consistently replicated, and the contribution of any identified locus appears small.[15] Progress in genomic medicine offers the hope that specific genes that confer an elevated risk of bipolar illness will be found.[16]

Genetic counseling of families with bipolar illness may be helpful, but of necessity, such counseling is based on premolecular and family studies. On the basis of family studies, the risk of bipolar disorder in the child or sibling of a person with the disease is about 10 percent.[13] Such information may be helpful for life planning, though even a risk of 10 percent may lead some potential life partners to think twice about continuing a relationship.

TREATMENT

ACUTE MANIA

Acute mania is a medical emergency. If a manic patient is not treated rapidly, he or she is liable to engage in activities that may endanger the patient's marriage or job and possibly the patient's life. Acutely manic persons may appear rational at one moment and yet be out of control the next. For example, a manic person who is driving at 110 miles an hour through the city may just have had a rational conversation with the family physician in which

the patient denied having delusions or hallucinations and seemed pleasant, even if speaking unusually rapidly. It is critical to obtain collateral information from relatives, friends, and coworkers about such a patient's behavior in recent days to supplement the clinical interview. Identified behavioral dangers are as much an indication for involuntary hospitalization of a patient as the patient's verbal expression of violent hallucinations or delusions.

Numerous effective treatments exist for acute mania (Table 2). Neuroleptic (antipsychotic) drugs are clearly effective in acute mania.[30] These drugs are not recommended for long-term prophylaxis because of the danger of tardive dyskinesia. In the acutely manic patient, these medications have the advantages of readily available parenteral as well as oral forms and of rapid onset of psychomotor inhibition, which may be lifesaving in the case of a violent or psychotic patient. These medications are generally detested by patients with milder disease, who often are more compliant with a regimen than are patients with severe mania. The new, atypical antipsychotic drugs (those without extrapyramidal side effects) are effective in compliant patients and also may pose lower risks of inducing depression than is the case with classic neuroleptic drugs. Parenteral preparations of the atypical antipsychotic drugs are becoming available. Some worrisome adverse effects of these drugs include weight gain, changes in lipid levels, and abnormalities in glucose tolerance.[31] Thus, a patient who had a good response to a classic neuroleptic in the past should probably be treated with the same drug when a recurrent manic episode occurs.

Research studies have shown that lithium, valproate, and carbamazepine have established efficacy in the treatment of acute mania and are effective in clinical practice as monotherapy for occasional episodes of mild mania in unusually compliant patients. Surveys of clinicans, however, have suggested that these drugs work too slowly in the great majority of patients with acute mania.[32] Treatment should generally be initiated, then, with either a typical or an atypical neuroleptic drug, with the addition of a mood stabilizer such as lithium, valproate, or carbamazepine as soon as compliance with oral therapy is assured.

BIPOLAR DEPRESSION

Bipolar depression (depressive episodes in a patient with bipolar illness) generally responds to tricyclic antidepressants, selective serotonin-reuptake inhibitors, and monoamine oxidase inhibitors.[33] The length of time before a response in a patient with bipolar depression is similar to that seen in those with unipolar depression, three to six weeks. However, treatment for bipolar depression must be carried out in the knowledge that antidepressant drugs may induce a switch from depression to mania. A patient with a history of at least one dangerous episode of mania that put the family or the patient's job at risk should probably not be treated with antidepressants, even if the patient continues to have residual low mood or low energy. However, patients who have had one diagnosed moderate episode of mania in which neither self-injury nor damage to the family occurred but who have had recurrent, crippling depression after the single manic episode will probably benefit from an antidepressant without sustaining undue risk.[33]

Some studies have suggested that relatively new antidepressants such as the selective serotonin-reuptake inhibitors and bupropion are less likely than older agents to induce mania in persons with bipolar depression,[34] but these studies have often been restricted to data on patients with very mild mania (bipolar II disorder), and the data should not be extrapolated to all patients with bipolar illness.[35,36] The n–3 fatty acids have been experimentally reported to be antidepressant in preliminary studies[37] and may represent a new direction for the treatment of bipolar disorder. Inositol is another natural substance that has been studied in bipolar depression.[38]

MOOD STABILIZERS AND PROPHYLAXIS

Lithium is the quintessential and classic mood stabilizer.[39] Lithium was developed when the regulations of the Food and Drug Administration (FDA) were less stringent than they are now, and the new agents to treat mania may be promoted as the only treatments that satisfy the current, more stringent standards of proof in clinical trials. However, for the past 50 years lithium has been shown to have antimanic efficacy, prophylactic efficacy in bipolar disorder, and some efficacy in prophylaxis against bipolar depression.[23] The drug has a narrow therapeutic index, and the blood levels in patients taking lithium must be monitored. Severe toxic effects and sometimes death can occur when renal excretion is impaired, even by such apparently innocent changes as the onset of diuretic treatment for hypertension. Progressive renal failure after decades of lithium use has been reported,[40] although some

Table 2. Drug Treatments for Mania and Bipolar Disorder.

Drug	Side Effects	Indication	Effectiveness	Study
Classic oral neuroleptics	Extrapyramidal syndrome, hypotension	Moderate-to-severe mania in patients with good compliance	Highly effective but poses risk of depression	Licht,[17] Littlejohn et al.[18]
Clozapine	Agranulocytosis	Inadequate responsiveness to other treatment	Highly effective	Suppes et al.[19]
Atypical neuroleptics	Diabetes and weight gain (olanzapine), hyperprolactinemia (risperidone), prolonged QTc interval (ziprasidone)	Extrapyramidal side effects and risk of tardive dyskinesia with typical neuroleptics	Established for moderate mania, but not for severe mania	Sanger et al.,[20] Vieta et al.,[21] Keck et al.[22]
Intramuscular neuroleptics	Extrapyramidal syndrome, hypotension	Noncompliance with oral agents	Highly effective but poses risk of depression	Littlejohn et al.[18]
Lithium	Polyuria, hypothyroidism, weight gain	Good compliance	Highly effective, slow onset, low risk of depression	Goodwin,[23] Jamison et al.[24]
Valproate	Rare hepatotoxic effects, tremor, weight gain	Good compliance	Highly effective, slow onset, low risk of depression	Bowden et al.,[25] Bowden et al.[26]
Carbamazepine	Rare hepatotoxic effects, rash	Good compliance	Few data available	Ketter et al.[27]
Clonazepam and lorazepam	Excessive sedation	Anxiety, psychomotor tension, insomnia	Questionable for core syndrome, useful as adjunct	Chouinard,[28] Lenox et al.[29]

have questioned the specificity of lithium as the causative agent in these cases.[41]

Carbamazepine was the anticonvulsant drug reported to be useful in the treatment of bipolar illness in the 1980s[42] — it was estimated that as much as half the sales of carbamazepine were for bipolar illness. Throughout that decade, many small studies reported on the therapeutic efficacy of carbamazepine as prophylaxis against mania, bipolar depression, and bipolar disorder, as monotherapy sometimes but often in addition to other treatment. This literature has lately been reevaluated in the light of the FDA's standards for the licensing of new anticonvulsant agents for use in the treatment of bipolar disorder, and the literature has sometimes been found wanting. However, a clinician must take into account the relatively long and successful clinical use of this compound.[27]

The first studies of valproate (valproic acid), another anticonvulsant agent, in treating bipolar illness came from outside the United States,[43] as was the case with carbamazepine. These early studies were criticized by U.S. physicians as being poorly controlled. However, when a U.S. pharmaceutical company, Abbott, reached an agreement with the FDA to patent a new formulation of valproic acid, a large-scale, controlled study was carried out,[25] leading to a profitable compound, divalproex sodium. Although some have viewed divalproex sodium as having a dubious pharmacologic advantage over valproic acid, and despite heavy advertising and promotion of its use, lithium still controls a large market share in the treatment of bipolar disorder, a situation that suggests either that psychiatrists are a stubborn lot or that lithium may have greater efficacy in the treatment of bipolar disorder than commercially sponsored studies would suggest.[44] A recent large study has suggested that lithium prophylaxis is much more effective than valproate prophylaxis in the prevention of suicide among patients with bipolar disorder.[45]

The success of carbamazepine and valproate and the development of new antiepileptic agents have led to the use of these drugs in treating bipolar disorder as well. Case reports and small studies have suggested that topiramate is effective in

bipolar illness, although a large study sponsored by Janssen Cilag found no difference in efficacy between topiramate and placebo, perhaps because mild, antidepressant-induced manias subsided in a large number of patients in the placebo group.[46] Lamotrigine has also been reported to have a positive effect in bipolar illness, particularly in the depressive phase. Clinicians have for many years regarded lithium, valproate, and carbamazepine as more successful in controlling the manic phase of bipolar disorder than the depressive phase, and a need exists for a drug to treat depression for use in this disorder. A large, company-sponsored study suggested that lamotrigine was more effective as prophylaxis against bipolar depression than lithium or placebo.[47] However, the size of the effect was small, and there was concern about whether a large number of patients who had not had a good response to lithium had been attracted to the study.

Benzodiazepines act on the benzodiazepine receptor of the γ-aminobutyric acid–benzodiazepine complex and are effective in status epilepticus, and they may be useful adjuncts in the treatment of mania because they reduce tension and improve sleep. However, they do not seem to have true antimanic efficacy.[28,29] Gabapentin has not been effective against mania in well-designed trials, despite early reports suggesting such an effect.[48] Zonisamide and felbamate, also new anticonvulsants, have been shown in some case reports to have efficacy in bipolar illness but have not yet been studied in a controlled fashion.[48]

Dopamine receptor–blocking drugs (neuroleptics) that are used in schizophrenia are also therapeutic in acute mania. A few studies have found these drugs efficacious in prophylaxis against bipolar disorder as well, but the risk of tardive dyskinesia has limited their use. Atypical neuroleptic drugs such as clozapine, olanzapine, risperidone, and ziprasidone have efficacy[49] in at least some phases of bipolar disorder. Such efficacy blurs the distinction between therapy with neuroleptic drugs to treat schizophrenia and mood-stabilizing therapy. Future studies of prophylaxis with atypical antipsychotic drugs may lead to an entirely new classification of mood-stabilizing agents, in comparison with antipsychotic agents.

Although treatment with lithium or an anticonvulsant agent provides remarkable prophylaxis over many years for many patients with bipolar illness, large numbers of patients with breakthrough episodes of mania and, even more common, breakthrough depression present at referral centers. The effectiveness of a polypharmacy approach — lithium plus anticonvulsant, two anticonvulsants, lithium plus an atypical neuroleptic, and occasionally lithium plus an antidepressant — is supported by some research data.[50]

The design of drug trials for bipolar illness has engendered an ethical controversy that will affect future trials.[51] A manic episode can be life-threatening to the patient, and it is the view of many psychiatrists and physicians that, given that effective treatment exists, patients with this illness should not be recruited for placebo-controlled trials. However, in most cases the FDA has insisted on placebo-controlled monotherapy trials for the registration of new compounds for use in psychiatry. Some statisticians support the FDA's position, calculating that without the use of a placebo control group, many patients would be exposed to poor treatment because a very large number of subjects would be needed to prove lack of efficacy of a new treatment as compared with the efficacy of an active control medication such as lithium.[52] These statistical calculations do not take into account the distortions that may be induced by the use of unrepresentative patient populations in placebo-controlled studies. One example is a large, rigorous study that compared the efficacy of valproate, lithium, and placebo in three randomized groups of patients with bipolar illness and showed no significant differences between the groups, apparently because only patients with mild forms of the disorder were recruited.[26]

PSYCHOLOGICAL ASPECTS

Surprisingly, studies have not identified a clear personality trait specific to patients with bipolar manic–depressive illness. Intuition may suggest that patients are labile, unstable, or perhaps seekers of novelty even when they are not manic or depressed. However, there is little evidence of specific personality characteristics.[53] Evidence suggests that the first episode of bipolar disorder often is associated with stress in the life of the patient — the classic stressful event may be a first love relationship.[54] However, most studies agree that subsequent manic episodes often tend to be unrelated to external events in the patient's life.

Most clinicians and some research data support the idea that sleep disturbance can trigger manic and depressive episodes in patients with bipolar illness,[55] although in one controlled study no thera-

peutic effect of social rhythms therapy was shown.[56] Clinicians generally advise patients with bipolar disorder to avoid late work shifts, late-night partying, and other events that disturb sleep.[56,57]

PATHOPHYSIOLOGY

NEUROCHEMICAL STUDIES

The discovery that lithium, a simple ion, had a considerable effect in terms of mood stabilization suggested that a straightforward biologic pathophysiology might easily be detected in manic–depressive illness — a concept that could lead to important biologic findings in other mental disorders and in human behavior in general. However, 2004 arrived without the discovery of a biologic diagnostic test or the identification of a specific pathophysiological abnormality in manic–depressive illness. In early studies, urine and spinal fluid were examined for abnormalities in metabolites of the chief monoamine neurotransmitters, neuroadrenalin, serotonin, and dopamine. The findings were difficult to replicate and, if replicated, turned out to be secondary to the hyperactivity typical of mania and the hypoactivity and weight loss typical of depression.[58]

The techniques of postmortem neurochemical analysis have developed in recent years as brain banks have acquired modern methods, including speedy removal of central nervous system tissue.[59] Despite the use of protocols with patients' informed consent that include antemortem diagnosis and exclude the recruitment of patients with severe systemic physical illness, information about a patient's mental state at time of death — whether the patient had depression, mania, or euthymia — is rarely obtained. Patients with bipolar illness who die at an advanced age are likely to have neurochemical abnormalities secondary to other brain disorders, including Alzheimer's disease, or to the effects of long-term drug treatment. Those who die at a younger age often have committed suicide during a period of acute stress that was unrelated to the specific diagnosis. Perhaps the most specific and replicable findings are those of Rajkowska et al.,[60] which suggest a reduction in neuronal and glial density in specific frontal brain regions post mortem in patients with bipolar illness.

Table 3 provides a selected sample of recent neurochemical findings in the central nervous system in bipolar disorder. The findings of abnormalities in the euthymic state may be particularly important, because they have the potential to reveal abnormalities that precede the manifestation of symptoms of the illness. Such markers are also less likely to be artifacts than to be secondary to changes in the patient's activity, sleep, appetite, and weight. Until such findings can be replicated multiple times and shown to be independent of the alterations in activity and weight that are characteristic of mania or depression, the phenomena should not be considered to be established. Owing to the difficulty of studying the brain in a living patient, the use of a specific treatment as a "pharmacologic bridge" remains a key strategy to understanding the neurochemistry of bipolar disorder. The development of such a pharmacologic bridge involves the selection of a candidate neurochemical abnormality[68] and the testing of its relevance with the use of a hypothesis-based clinical intervention.[69]

NEUROIMAGING AND NEUROANATOMICAL STUDIES

The increasing sophistication of techniques to measure the anatomy and function of the human brain with the use of neuroimaging has not been ignored in the study of bipolar disorder. Even though computed tomography and magnetic resonance imaging (MRI) are limited to structural findings, functional MRI and positron-emission tomography (PET) can provide information about function. Most of the imaging studies in bipolar disorder are small, because of both the cost and the difficulty involved in studying patients who are either manic or depressed; to date, the ability to replicate results has been poor (Table 3).[70] One promising report noted decreased volume of gray matter and decreased blood flow in the subgenual prefrontal cortex of patients with bipolar illness, as compared with persons without this illness.[67] The prefrontal cortex is known to be involved in emotional responses, and its neurochemistry is affected by psychotropic drugs. At present, neither neuronal imaging nor neurochemical studies can provide a helpful answer to the relative of a person in whom bipolar illness is suspected who asks if there is a biologic test that can establish the diagnosis.

MECHANISM OF ACTION OF LITHIUM AND OTHER MOOD STABILIZERS

Lithium has a myriad of biochemical and biologic effects, although many of them occur only at toxic concentrations. One way to frame the biologic effects of lithium is to examine these effects as they came to be understood over the past half-century of

Table 3. Neurochemical and Imaging Findings in Bipolar Disorder.*

Focus of Study	Finding	Possible Implication	Study
B-lymphoblast cell lines	Increased intracellular Ca^{2+} in a subgroup of patients	Abnormal intracellular regulation	Yoon et al.[61]
Binding of VMAT type 2 in thalamus and ventral midbrain, studied with PET in vivo	Increased VMAT	Increased serotonin innervation	Zubieta et al.[62]
Postmortem brain tissue (prefrontal cortex and cerebellum), studied with immunohistochemical analysis, RT-PCR, and Western blot	Decrease in brain reelin	Abnormality of brain extracellular matrix	Guidotti et al.[63]
Dorsolateral prefrontal cortex, studied with magnetic resonance spectroscopy in vivo	Decreased cortical *N*-acetyl aspartate	Decreased neuronal density or dysfunction	Winsberg et al.[64]
Postmortem cortex studied with gas chromatography	Decreased brain inositol	Deficient second-messenger signaling	Shimon et al.[65]
Postmortem dorsolateral prefrontal cortex layer III, studied with the use of morphometric, three-dimensional cell counting	Reduced glial density (fewer but larger cells) in cortex	Abnormal neurologic development without gliosis	Rajkowska et al.[60]
Lymphoblastoid cell lines	Reduced inositol monophosphatase	Abnormal phosphatidylinositol second-messenger signaling	Shamir et al.[66]
Patients with familial bipolar depression, studied with MRI and PET	Decreased gray matter and blood flow in subgenual prefrontal cortex	Abnormal emotional responsiveness to social stimuli	Drevets et al.[67]

* VMAT denotes vesicular monoamine transporter, PET positron-emission tomography, RT-PCR reverse-transcriptase polymerase chain reaction, and MRI magnetic resonance imaging.

the development of neuroscience. The central focus in neuroscience has shifted repeatedly during this time, and lithium appears to have at least one major effect according to each focus (Table 4).

Lithium inhibits the accumulation of cyclic adenosine monophosphate (cAMP),[73] perhaps at the level of G proteins, which act to convey the signal between the receptors and adenylate cyclase.[78] Lithium may down-regulate second-messenger systems that are associated with cAMP–linked receptors. Lithium inhibits the activity of inositol monophosphatase,[74] resulting in inositol depletion, an effect that could down-regulate second-messenger systems that are linked to the phosphatidylinositol cycle. Although these two potential actions of lithium were of interest in the past, neither has led to the successful development of new drugs.[79] Newly proposed mechanisms for the action of lithium include the inhibition of glycogen synthase kinase-3 beta (GSK-3β),[80] the inhibition of binding of serotonin (5–HT) to 5–HT_{1B} receptors,[81] effects on glutamate uptake and release,[82] and an increase in the levels of the neuroprotective protein bcl-2.[77] The principle of Occam's razor would suggest that only one of these biochemical effects will emerge as the mechanism for the effect of lithium on mood. However, a better understanding of how lithium works would probably serve as a rational basis for the development of new drugs.

Mood stabilizers other than lithium include anticonvulsants, numerous biochemical actions of which involve voltage-activated sodium channels, and γ-aminobutyric acid.[83] Valproate shares some reported effects with lithium — for example, the inhibition of GSK-3β and the increase in bcl-2.[84] Recently, Williams et al.[85] reported that lithium, valproate, and carbamazapine have common effects on neuronal growth cones that are reversible by inositol — a finding that supports the classic inositol-depletion hypothesis.

SUMMARY

The evidence of a clear genetic predisposition to bipolar illness has led to important efforts in gene discovery, and several linkage studies have pro-

Table 4. Focus of Neuroscientific Studies and the History of Understanding the Mechanism of Action of Lithium.*

Period	Focus	Finding about Lithium	Study
1965–1975	Monoamine metabolites	Increases deaminated norepinephrine metabolites	Knapp and Mandell[71]
1976–1985	Neurotransmitter receptors	Prevents dopamine-receptor supersensitivity	Pert et al.[72]
1986–1995	Second messengers		
	cAMP	Inhibits adenylate cyclase	Ebstein et al.[73]
	Phosphatidylinositol cycle	Inhibits inositol monophosphatase	Berridge et al.[74]
1996–2000	Third messengers		
	Immediate early-response genes	Affects *c-fos*, *c-jun*	Leslie and Moorman[75]
	Response elements	Increases CREB DNA binding	Jope et al.[76]
2000–present	Neuroprotection and neurogenesis	Increases levels of neuroprotective protein bcl-2	Manji et al.[77]

* cAMP denotes cyclic AMP, and CREB cyclic AMP–responsive element–binding protein.

duced similar results. However, these results are not sufficiently robust to be used in genetic counseling. New drugs, such as valproic acid and lamotrigine, are effective. These drugs are useful alternatives for patients in whom adverse effects occur with lithium or in whom the response to lithium is inadequate, but no drug seems more effective than lithium for the majority of patients with bipolar illness. Although the search for evidence of abnormalities in neurochemical and neuroimaging studies remains promising, diagnostic markers that would have clinical relevance have still to be discovered.

A new diagnostic tendency to view milder conditions that include mood swings as variants of bipolar illness may lead to more effective treatment for some affected patients, often with lithium or valproate, but the use of these agents in mild variants of the disorder remains unsupported by strong biologic or clinical data. For this reason, clinicians should be careful to avoid misdiagnosing psychological or social phenomena as bipolar illness. Increasing evidence for the efficacy of new atypical antipsychotic drugs in the treatment of and prophylaxis against bipolar illness has provided a major treatment alternative that may, in the future, blur the diagnostic and therapeutic boundaries between bipolar illness and schizophrenia. However, the emerging adverse effects of these new compounds cannot be ignored.

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