Bipolar Disorder as Cell Membrane Dysfunction. Progress Toward Integrative Management

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Abstract

Bipolar disorder (BD) is characterized by periods of abnormally elevated mood (mania) that cycle with abnormally lowered mood (depression). Multiple structural, metabolic, and biochemical abnormalities are evident in the brain's cortex, subcortex, and deeper regions. This disorder is highly genetically conditioned but also highly susceptible to environmental stressors: prenatal or perinatal insults, childhood sexual or physical abuse, challenging life events, substance abuse, and other toxic chemical exposures. Its high morbidity, lost productivity, and suicide risk place a great toll on society. Since World War II, BD has been steadily worsening with earlier age of onset, greater intensity of symptoms, and development of drug resistance. Incidence in children is rising and misdiagnosis is common. Disciplined management of the many risk factors is essential, including cognitive psychotherapy and support from family and community. Lithium has been the foundational treatment, followed by valproate and other mood stabilizers, antidepressants, and anticonvulsants. Several single-nutrient and multinutrient supplements have also proven beneficial. Controlled, double-blind trials show multinutrient combinations of vitamins, minerals, orthomolecules, herbals, and the omega-3 fatty acids EPA and DHA to be effective monotherapy. The molecular action of lithium and valproate converge with nutrients on the level of the cell membrane and its molecular signal transduction systems. This emergent, unified rationale presages effective integrative management of bipolar disorder.

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Introduction

Bipolar disorder (BD; manic depressive illness) is a disorder of the brain characterized by extreme changes in mood, energy, thinking, and behavior. It is one of the earliest identified mental disorders, recognized as early as the time of Hippocrates in 400 BC.[1] Bipolar disorder has left its mark on history – prominent individuals who had symptoms of BD include Winston Churchill, Ernest Hemingway, Abraham Lincoln, Theodore Roosevelt, and Virginia Woolf.[2,3] It is on the increase, especially among children and adolescents. But despite a considerable existing knowledge base, BD remains one of the most difficult disorders to diagnose, classify, and manage.[4]

Bipolar disorder is a major cause of disability and premature death from suicide, yet it is greatly underdiagnosed, and inappropriate pharmacotherapy often worsens the symptomatology.[5] The existing pharmacotherapies can have devastatingly adverse effects, yet BD management has received surprisingly minimal priority compared with unipolar ("major") depression. This review covers the clinical features of BD and current available therapies. Recent research advances

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are reviewed and a framework proposed for a more advanced, integrated approach to management.

Diagnosis, Prevalence, Progression

During the time of Hippocrates, this illness was seen as two disorders: mania and melancholia.[1] Its recognition as a single disorder dates to 1921, when the term manic-depressive insanity was coined by Emil Kraepelin, who made significant contributions to classifying the various psychotic disorders.[6] Estimates of the current lifetime prevalence rate of BD vary widely, from 1 percent to as high as 3.7 percent worldwide for the entire bipolar spectrum.[5,7] Among children and adolescents the incidence has been spiraling upward for the past half century.[8]

Bipolar disorder can manifest at almost any age, but the peak period of onset is adolescence (15-19 years).[9] Later onset suggests a lesser familial genetic contribution. In the United States prevalence appears similar across ethnicities, but misdiagnoses (a general problem with this disorder) are even more frequent in the African American and Hispanic populations.[9]

Bipolar disorder has significant morbidity and mortality; the illness can ravage the patient's employment status and personal relationships, and sexuality and financial management capacities can become distorted. Lifetime risk for suicide is 19 percent, a rate comparable to the mortality rates for some heart diseases and cancers.[9]

Diagnosis and Subtypes

The formal diagnosis of BD is complicated and is somewhat different in the United States than Europe. Following the U.S. Diagnostic and Statistical Manual 4th Edition (DSM-IV),[10] the bipolar disorders involve the presence (or history) of manic episodes, mixed episodes, or hypomanic episodes, usually accompanied by major depressive episodes. The occurrence of mania distinguishes bipolar disorder from other depressive disorders, including major depressive disorder commonly known as clinical depression.

The U.S. DSM-IV recognizes four subcategories of BD:[10]

- Bipolar I disorder – characterized by one or more manic or mixed episodes usually accompanied by major depressive episodes. There can be psychotic features, catatonic features, or postpartum onset. The pattern can be predominantly seasonal or involve rapid cycling. During manic episodes violent behavior is common, such as child or spousal abuse or other antisocial behavior. Some 10-15 percent of these individuals attempt suicide. Bipolar I is highly heritable among first-degree relatives.

- Bipolar II disorder – characterized by one or more major depressive episodes accompanied by at least one hypomanic episode. As with Bipolar I, this disorder is highly heritable and a similar percentage attempt suicide.

- Cyclothymic disorder – characterized by at least two years of numerous periods of hypomanic symptoms that do not meet criteria for a manic episode, and numerous periods of depressive symptoms that do not meet criteria for a major depressive episode. This is a chronic, fluctuating mood disturbance. This disorder often begins in adolescence or early adult life, and has a 15-50 percent risk of subsequent progression to bipolar I or II disorder. Often a first-degree family link exists.

- "Bipolar disorder not otherwise specified" – is a catch-all category for cases with bipolar features that do not meet criteria for the three foregoing categories, or for which there is inadequate or contradictory information. For more detail, refer to the DSM-IV.

Criteria for Defining Episodes[10]

The DSM-IV defines a major depressive episode as a minimum two-week period during which there is depressed mood or loss of interest in nearly all activities. Other symptoms must be involved, such as changes in appetite, sleep, or psychomotor activity; decreased energy; feelings of worthlessness or guilt; difficulty thinking,

concentrating, or making decisions; or recurrent thoughts of death or suicidal ideation. The episode must be accompanied by clinically significant distress or impairment in social, occupational, or other important areas of functioning.

A manic episode has a minimum one-week duration in which there is abnormally and persistently elevated, expansive, or irritable mood. Elevated mood is euphoric or excessively high for that individual. Labile alternation between euphoria and irritability is frequently seen. Other symptoms must be present, such as inflated self-esteem or grandiosity, less need for sleep, flight of ideas, distractibility, psychomotor agitation, and self-destructive behavior. Manic episodes are also characterized by "unceasing and indiscriminate" enthusiasm for interpersonal, sexual, or occupational interactions.

A hypomanic episode lasts a maximum of four days, during which time mania is evident. The episode must not be severe enough to cause marked functional impairment or require hospitalization. Symptoms can resemble a manic episode except that delusions, hallucinations, and psychosis cannot be present.

A mixed episode involves at least one week during which the criteria are met for both a manic episode and a major depressive episode nearly every day.

The Bipolar Spectrum

Over the past decade it has become acceptable to view BD as a continuum of symptom severity, ranging from features of relatively mild depression and brief hypomania to debilitating patterns of rapid cycling or frequent mania with psychotic features. Individual patient symptoms can vary in degree of polarity, severity from episode to episode, duration of episodes, and cycling frequency. Many physicians, some very experienced with BD, have trouble distinguishing among the subcategories of BD, and the concept of a bipolar spectrum often has more clinical relevance than bipolar I versus bipolar II.[1]

Conditions Comorbid with Bipolar Disorder

The most frequent comorbid conditions with BD are anxiety-related,[11] such as panic or obsessive-compulsive disorder;[12] substance abuse; so-called disruptive behavior conditions, such as attention deficit disorder and oppositional-defiant disorder;[13] and, among women, post-traumatic stress disorder (PTSD) and eating disorders.[9] Advisedly, patients presenting with any of these other comorbid conditions should be assessed for possible BD.

BD is much more common in multiple sclerosis patients than in the general population.[14] Other significant comorbidities with BD are asthma[15] and possibly migraine.[16]

Bipolar disorder is linked with schizophrenia (SCZ) through symptomatic, genetic, and pathophysiological similarities.[7] Many neurotransmitter abnormalities seen in SCZ, most notably enhanced sensitivity to dopamine and dopamine agonists, are seen in BD.[1] Also, newer atypical antipsychotics approved for SCZ (olanzapine, risperidone, quetiapine) are proving useful for BD.[1]

BD also has substantial overlap with major depressive disorder (MDD).[10] Just as the pathophysiologies of BD and SCZ do not show marked differences, a 1997 review of studies that directly compared the biological features of unipolar depression with bipolar depression was unable to find consistent differences.[17] Abnormalities of serotoninergic actions are seen in MDD and BD as well as SCZ.[1]

Family studies also suggest linkages between schizophrenia, bipolar disorder, and major depressive disorder. Many families, followed through several generations, demonstrate a prevalence of all three diagnoses.[18] Clinically, many patients show features of two or even all three of these psychiatric illnesses.[19] Mechanistic research suggests shared cell membrane dysfunctions.[18] Proponents of a "continuum" in the major affective disorders suggest a continuum ranging from unipolar to bipolar disorder, through schizoaffective psychosis, all the way to schizophrenia.[1,18]

Rising Incidence among Children and Adolescents

This disorder has probably always afflicted children – in particular the biographies of Beethoven, Newton, and Dickens reveal severe, debilitating, and recurrent mood swings beginning during childhood.[8] In the United States, each generation since World War II has had a higher incidence and earlier age of onset of BD.[8] On average, children with BD experience their first episode of illness 5-10 years earlier than did their parents' generation.[8] Once the illness starts it tends to get worse until treatment is begun.

Children with BD often experience rapid cycling of mood states several times daily.[2] This generally manifests as ongoing, chronic irritability with a few hours of wellness between episodes.[8] The disorder in children is likely more severe than in adults, with many children manic and depressed at the same time and ill for years without intervening periods of wellness.[2]

Adolescents tend to manifest a symptom pattern closer to adult BD. For many, a traumatic event triggers their first episode. Puberty carries increased risk, and in girls the onset of menses may trigger the illness. An estimated 10-15 percent of adolescents with recurrent major depressive episodes develop bipolar I disorder.[8] In this population BD is often misdiagnosed as borderline personality disorder, post-traumatic stress disorder, or schizophrenia.

In the United States an estimated one million or more minors diagnosed with major depression may actually be experiencing early onset BD.[8] The Child and Adolescent Bipolar Foundation estimates a "significant number of children" diagnosed with ADHD actually have BD.[8]

Children and juveniles with BD are at high risk for developing addictions to drugs and alcohol. Those with mania face a heightened risk for trauma exposure (violence, rape, physical or sexual abuse, or other events outside the range of normal human experience).[13] This scenario underscores the harsh reality of childhood BD and the need for improved diagnosis and management.

The Pathophysiology of Bipolar Disorder

The new generation of imaging instrumentation has revolutionized brain research. These macroscopic findings are being integrated with the more traditional microscopic pathological findings to derive clinically relevant understanding of the structural, metabolic, and biochemical abnormalities that encompass bipolar disorder.[20-23]

Structural Abnormalities

The BD brain shows structural abnormalities on a regional basis,[20,22,23] with zones within the cortical, subcortical, limbic, and other regions affected. Best documented is the prefrontal cortex.

Prefrontal Cortex

Within the prefrontal cortex the anterior cingulate cortex areas (ACCA) are known to be centrally involved in mood disorders. The ACCA are thought to be at the functional interface of emotion, cognition, drive, and motor control.[20] Magnetic resonance imaging(MRI) by Drevets and colleagues revealed gray matter volume was reduced 25-40 percent in the ACCA in BD.[20,24]

Drevets' group investigated further, using histological morphometric cell-counting techniques. They found a trend toward reduced numbers of glia "support" cells but not of neurons.[25] Several subsequent studies established that glial cell numbers were reduced, with caveats that the changes applied specifically to familial but not non-familial BD.[20] Abnormal neuron appearance was evident, but without loss in numbers. Histochemical localization of synaptic and dendritic proteins found reduced amounts for most of them, indicating synaptic and probably also dendrite pathology. In sum, the prefrontal cortex shows "cytoarchitectural" circuit abnormalities specific to BD.[20] Other regions of the prefrontal cortex were implicated in mood disorders on functional and structural grounds. Similar changes were evident as in the ACCA.[20] Glial cell loss was again seen, together with neuronal changes and overall circuit abnormalities.

Hippocampal Formation

The hippocampus has also been implicated in mood disorders. Several MRI studies found significantly smaller hippocampal volumes in BD patients.[20] Histological studies are equivocal on cell changes, but histochemistry suggests subtle synaptic and dendritic abnormalities may be present.[20,26]

Subcortical Regions

In order to test the neurotransmitter imbalance theories of depression and bipolar disorder, cell bodies within the subcortical zones that secrete serotonin and catecholamines were quantified. To date several studies reveal no consistent changes.[20] Subtle network or circuitry abnormalities cannot yet be ruled out.

Within the deep subcortical white matter lie the most consistent pathologic findings of BD – white matter hyperintensities (WMH). More than 30 MRI or computed tomography (CT) studies have imaged such small areas, where the signal intensity is high relative to the surrounding tissue.[20,22] Most often seen in aging and cerebrovascular disorders, WMH are extremely rare in healthy individuals under the age of 30. Demyelination, glial cell inflammation, or axonal loss linked to brain ischemia and infarction contribute to WMH.

The risk for having WMH was estimated to be 3-7 times higher in BD patients of all ages.[20,22] When present they are generally observed early in the course of illness, although most patients with BD do not have WMH, nor is there any clear association with medications. However, toxic risk factors preferentially associated with BD such as cigarette smoking, excessive alcohol consumption, and other substance abuse (see below), can combine with cardiovascular risk factors (such as hypertension) and lead to cerebrovascular lesions and WMH.[22]

Cerebellum

Decreased size and anomalies of blood volume have been reported in the cerebellum of BD patients.[22,23] CT and MRI studies suggest cerebellar atrophy tending to be more extreme in brains with greater numbers of recorded BD episodes. Cerebellar abnormalities could contribute to dysregulation of limbic and cortical regions that partly determine mood.

Metabolic Abnormalities

Positron emission tomography (PET) uses exogenous fluorine18-deoxyglucose (18-FDG) to assess the cerebral metabolic rate for glucose, and oxygen-15-water (15-H2O) to measure cerebral blood flow. Single photon emission computed tomography (SPECT) uses exogenous labeled technetium to quantify cerebral perfusion. Functional MRI (fMRI) also yields neurophysiological data related to cerebral activity. These three approaches implicate metabolic abnormalities of the cortex in depression associated with BD.[27]

PET and SPECT studies demonstrate low glucose metabolism and blood flow in the cortex (prefrontal and paralimbic) of moderately to severely depressed BD patients.[27] This finding is common to depressive disorders regardless of etiology (primary versus secondary) or subtype (unipolar versus bipolar).

In contrast to low cortical metabolism, subcortical paralimbic structures such as the ventral striatum, thalamus, and amygdala showed abnormally high metabolism in moderately to severely depressed BD patients.[27] This pattern of cortical hypofunction with paralimbic overactivity, or vice versa, is consistent with a corticolimbic dysregulation model of depression.[28]

Most of the glucose metabolism and blood flow abnormalities seen in depressed BD patients via imaging are not seen in unmedicated, euthymic patients, so are most likely mood related. In treatment-resistant BD, the cerebellum may show increased metabolism independent of mood state.[29]

Biochemical Abnormalities

MRS (magnetic resonance spectroscopy) identifies and quantifies metabolites and other substances in the working brain. Most MRS studies of BD have used proton detection (1H) or phosphorus detection (31P). 1H-MRS readily quantifies total choline, which includes choline and

phosphocholine, but is likely dominated by membrane phosphatidylcholine (PC). 1H-MRS studies show lowered total choline in the BD brain.[30] Interestingly, this total choline measure tends to increase with successful response to treatment.[31]

1H-MRS also visualizes N-acetylaspartate (NAA), a compound believed to represent neuronal density and integrity. NAA measured low in the prefrontal cortex of euthymic, unmedicated adult and medicated juvenile BD patients, consistent with the decrease of gray matter in this region.[27] Patients under treatment with lithium tended toward normalization both of NAA and gray matter density in this region.[32,33]

31P-MRS visualizes phosphates including phosphocreatine, and phosphomonoesters (PMEs) such as phosphoethanolamine, phosphocholine, phosphoserine, and inositol-1-monophosphate. In a comprehensive series of 31P-MRS studies, levels of frontal lobe PMEs in depressed BD patients measured significantly higher than healthy controls, while euthymic (asymptomatic) BD patients had significantly fewer PMEs.[27] Since the PMEs are virtually all membrane phospholipid metabolites, this pattern is consistent with altered membrane metabolism and possible membrane signal transduction malfunction.

Energetic Abnormalities

31P-MRS studies demonstrate significantly decreased phosphocreatine in the frontal lobes of BD patients.[34] Phosphocreatine is a cellular energy reservoir, degraded to ATP during times of high energy demand. Phosphocreatine levels reflect general cellular energy status, and decreased levels are suggestive of hypometabolism. One explanation for this lowered energetic status is mitochondrial dysfunction.[31]

Other findings suggesting abnormal energetics in BD are: (1) lowered pH by 31P-MRS in frontal lobes, consistent with lactate accumulation;[35] and (2) increased lactate and glutamate/glutamine by 1H-MRS in drug-naive BD patients compared with healthy subjects.[31] Kato and Kato suggest these energetic abnormalities represent mitochondrial dysfunction in the BD brain.[34]

Building on this suggestion, Modica-Napolitano and Renshaw used rat mitochondria *in vitro* to show that PME buildup can inhibit mitochondrial function.[31] At this point there is no convincing evidence to directly implicate mitochondrial failure in BD causation, but the topic deserves further exploration.

Heritability and Other Risk Factors

Generally accepted risk factors for BD include a family history of BD, a history of substance abuse, thyroid disturbances, and an existing anxiety disorder diagnosis.[7] Women are also prone to develop BD after childbirth.

Bipolar disorder is substantially conditioned by genetic background, although environmental influences are also confirmed to be important in the disorder's emergence, severity, and patterns of cycling. Its average age of onset has shortened, from the early 30s to the late teens in one generation, and one case in five may begin with mania in childhood.[3]

Genetic Susceptibility

The heritability of BD is quite high. From twin studies, the concordance rate is estimated at 57 percent for monozygous twins and 14 percent for dizygotic twins.[9] These rates are similar regardless of whether the twins are raised together or separately. For a hypothetical 100-percent genetic disorder, the concordance rates would be 100 percent. The possible continuity of the BD spectrum with the SCZ spectrum is epitomized by a set of monozygotic triplets in which one had chronic SCZ, one had a schizoaffective disorder, and one had BD.[9] About 90 percent of bipolar subjects have at least one close relative with a mood disorder.[3]

Parental inheritance is important in BD. Having one parent who is bipolar entails a 10-30 percent risk of developing the condition, while having both parents with BD elevates the risk to as high as 70 percent;[8] having a bipolar sibling carries a 20-percent risk. This disorder is very likely multigenic, possibly involving as many as 10 susceptibility genes, the interactions of which generate a gradient of susceptibility.[9]

Each generation since World War II has seen increased incidence and earlier onset of BD (and MDD).[8] DePaulo and colleagues (cited in Post et al[36]) observed a 9-13 year earlier onset of BD in the offspring of parents with BD and suggest this is due to genetic anticipation. Anticipation refers to the increase in disease severity or decrease in age of onset in succeeding generations. Another contribution to genetic anticipation could come from men with either bipolar or unipolar depressive disorders (an estimated 10 percent of the population) marrying women with similar disorders (up to 20 percent of the population).

A multigenic heritability with complex pattern of penetrance would be compatible with some BD cases being late-onset and others being early-onset. Simplistically, the heavier the genetic load the earlier the onset and the lower the threshold for environmental triggering.[36]

Prenatal or Perinatal Insult

Stressful events during gestation and the neonatal period can have pivotal effects on the later health of the offspring. A long-term study of more than 5,000 subjects born in 1946 found obstetric complications to be linked to later mood disorders, especially the earlier-onset and more severe forms.[37] Rush reviewed several studies that link prenatal and perinatal complications with BD.[9]

Stress during pregnancy results in fetal exposure to chronic high levels of endogenous maternal corticosteroids. In humans the resulting adverse outcomes can be multiple, and include behavioral abnormalities with risk for schizophrenia and depression in later life.[38] Neonatal rat pups deprived of their mother develop lifelong high cortisol levels, increased anxiety behaviors, and a proneness to alcohol and cocaine addiction (in rodents, "self-administration").[36] Cell loss can occur within the brain, and growth factors, enzymes, and pathways linked to neuronal maturation and brain plasticity become imbalanced (Xing, cited in Post et al[36]). Susceptibility to seizures in adulthood is enhanced.[38]

Like prenatal stress, postnatal stress raises the risk for mood disorders in later life. Chronically high endogenous corticosteroid levels that develop from overactivation of the neonate's own stress-coping mechanisms can inhibit neurogenesis and interfere with the establishment of circuit architecture.[38]

Stress and Other Psychosocial Factors

Social environment and major life stressors are consistently implicated in BD. Latent BD can be activated by stressful life events such as death or divorce. Recurrence rates and time to recovery can be tripled compared to nonstressed patients.[9] Goal attainment stress, even from an outwardly positive event such as starting college, can have negative consequences,[3] and a lack of social support can worsen depression symptoms and lengthen recovery time.[9]

Early-life psychosocial stressors interact negatively with the neurobiology of BD. Bipolar individuals who report early (childhood or adolescent) physical or sexual abuse, compared to other bipolars without such history, have earlier illness onset, more rapid cycling patterns, greater intensity of manic and depressive episodes, shorter euthymic periods, and an increased incidence of serious suicide attempts.[36]

As first described by Kraepelin and reviewed by Post et al,[36] the number of prior BD episodes is a risk factor for episode recurrence. Patients with earlier onset and more prior episodes also may score more poorly on cognitive tasks when tested in the euthymic state.[39] Earlier illness onset, with or without early stressful life events, places the patient at greater risk for substance abuse, increased comorbidities, social and employment disabilities, and even increased risk for neurophysiological impairment.[36]

An "extreme affective dysregulation" resembling bipolar disorder is increasingly being seen in children as young as 2-4 years.[36] This can include temper tantrums, irritability, impulsiveness, aggression, hyperactivity, and poor attention. These symptoms may not meet the DSM-IV criteria for bipolar disorder, yet such children are likely at higher risk for later BD, particularly if they express extreme mood swings.[40]

Physiological Risk Factors

An existing medical condition or intervention can trigger BD expression. In women the postpartum period brings particular risk for depression and other mood changes, including mania. Low thyroid function has repeatedly been linked to BD, and hypothyroidism is a likely risk factor for rapid cycling.[36] Patients with BD have higher rates of positive anti-thyroid antibody titers compared with non-BD patients.[9]

Patients who develop cyclothymia, a condition similar to BD but less severe, are at very high risk for full-blown BD. In a prospective study, 35 percent of cyclothymic patients developed full hypomanic, manic, or depressive episodes during a drug-free follow-up period of up to three years.[7] Cyclothymic patients must be managed as pre-bipolar candidates.

Inadequate blood sugar supply to the brain (hypoglycemia, really a subtype of dysglycemia) is a frequent finding in the medical history of BD patients.[41] Hypoglycemia is notoriously multisymptomatic, but its major symptoms include many that also characterize bipolar disorder – mood swings, bizarre behavior, depression, anxiety, and irritability.

Common and uncommon risk factors can interact. Head injury, even when associated with minimal trauma, can lead to affective psychoses and schizophrenia.[42] Animal studies indicate molecular events controlled by brain derived neurotrophic factor (BDNF) are important in shaping the capacity of the brain to recover from injury. An experimental model of rats subjected to controlled brain injury demonstrated that a high-fat and -sucrose diet (as consumed in most industrialized societies) reduces levels of BDNF and leads to impairments in neuronal and behavioral plasticity without frank neurodegeneration.[43] Implications for the pathobiology of BD are obvious and perhaps give cause for alarm.

Substance Abuse

Substance abuse is a particularly common and problematic condition for BD individuals. More than half abuse alcohol, amphetamines, cocaine, or some other substance.[9] The relative risk for a BD patient to be a drug abuser is 6.6 times that of a non-BD subject.[44] Undoubtedly, in some cases substance abuse is an effort to manage symptoms – cocaine to create hypomania during depressive periods or alcohol to quiet racing thought patterns during a manic episode.[7] Some individuals may possess a genetic vulnerability or other risk factor common to both BD and substance abuse. In any case, substance abuse can worsen the course of BD and has been associated with earlier onset of the disorder.[45]

Chronic substance abuse can mimic almost any psychiatric disorder, further complicating the already difficult diagnosis of BD. Stimulant abuse can produce symptoms virtually identical to mania or hypomania, while stimulant withdrawal results in significant depressive symptomatology. Alcohol abuse together with BD doubles the risk of suicide.[9]

Substance abuse can also have a transgenerational adverse effect.[36] For example, children born to cocaine abusers are at higher risk for perinatal stroke, abruptioplacentae, and seizures.[46] Examining long-term risk, these children are more likely to progress from perinatal irritability to hyperactivity/ADHD, and on to conduct disorder, mania, or other affective illness, setting up a potentially vicious cycle.[38]

Toxic Environmental Chemical Exposure

In 1989 a group from the University of Texas published a study on Vietnam War veterans that correlated psychiatric problems with exposures to Agent Orange (2,4,5-trichloro-phenoxyacetic acid, 2,4-dichlorophenoxyacetic acid, tetrachlorodibenzodioxin), a highly toxic chemical that the United States used extensively as a defoliant in Vietnam.[47] Those veterans who reported high Agent Orange exposure scored significantly higher on scales of depression and mania.

Manic symptoms can be secondary to an underlying medical disorder and/or drug toxicity, rather than caused by BP.[9] Secondary mania may be differentiated from the mania of BD by having later onset (median age 41 years) and a negative family history of BD.

Current Medical Management of Bipolar Disorder

Among psychiatric illnesses, bipolar disorder ranks second only to major unipolar depression as a cause of global disability. Bipolar patients may spend as much as 20 percent of their lives in episodes,[48] most of this lost time taken up by depression.[49] Between episodes, some 30-60 percent suffer psychosocial impairment.[50] Even for those patients under apparent control, the relapse rates range as high as 40 percent in one year, 60 percent in two years, and 73 percent in five or more years.[51] While certain behavioral interventions such as cognitive-behavior therapy [52] and cell membrane nutrients have shown promise,[53,54] the medical management of BD remains overwhelmingly pharmacological. The depression of BD is under-researched in comparison to unipolar depression or the mania of BD, and many of the drugs used are transferred from other applications. Pharmacotherapy of BD rests mainly on three classes of drugs: mood stabilizers (especially lithium), anticonvulsants, and antidepressants.

Mood Stabilizers

The term mood stabilizer is functional rather than categorical, since drugs of several chemical types can be useful for this purpose in BD. These are drugs that (ideally) help prevent and/or treat manias or depressions without exacerbating or initiating them.[4]

Lithium

Lithium, a naturally occurring mineral prescribed as its carbonate salt, remains the single most effective and reliable drug treatment for BD. Lithium is generally effective as maintenance therapy for preventing mania and depression, and has shown benefit as monotherapy for BD in a number of double-blind trials.[54,55] Estimates of lithium's effectiveness in BD vary broadly, ranging from 36-80 percent success.[4] It remains the primary mood stabilizer for BD, even though as monotherapy for the depression of BD it is far from ideal.

Lithium has a narrow therapeutic range and overdoses can be fatal. Common side-effects include diarrhea, polyuria, tremor, acne, taste distortion, sedation, cognitive dulling, goiter, and weight gain. Laboratory monitoring is required as long-term treatment can cause renal, thyroid, and cardiovascular toxicity,[4] and lithium is a teratogen.[54] Lithium also poses a certain risk of triggering mania during depression. If this occurs, it should be gradually discontinued as its abrupt discontinuation causes a "rebound" effect with an estimated 28-times elevated risk for a new episode.[4]

Lithium therapy frequently precipitates hypothyroidism, an effect that seems to afflict more than half of rapid-cycling patients.[56] Such patients tend to manifest marked elevation of thyroid stimulating hormone (TSH) when placed on lithium. Bipolar symptomatology in this population will often respond positively to high doses of thyroid hormone replacement, even when refractory to conventional drug treatment.[57]

Several subgroups of patients typically do not respond well to lithium, including those with mixed states, rapid cycling, comorbid substance abuse, or personality disorders, and it can become less effective over time. Compliance is also difficult due to the many side effects. Data from one health maintenance organization indicated 50 percent of patients stop lithium within 10 weeks.[4]

Anticonvulsants

Valproate, an anticonvulsant, is a mood stabilizer used as an alternative or adjunct to lithium. Valproate typically is not effective monotherapy or prophylaxis for BD, but seems effective for acute mania.[54,55] A double-blind trial indicated that when taken along with lithium it can significantly benefit the depression of BD.[50] Valproate's adverse effects include weight gain, sedation, hair loss, and nausea. It can cause blood dyscrasias or polycystic ovary disease, liver toxicity (rarely), and is a teratogen.[54]

Valproate is believed to be less toxic than lithium, but laboratory monitoring is required. It seemingly works better than lithium for patients with mixed states or rapid cycling.[54] Loading-dose strategies have been developed that may produce

more rapid symptom control than either gradual valproate dose escalation or lithium therapy. Valproate depletes the energy-yielding nutrient carnitine, so this should be supplemented to patients taking this medication.[58]

The anticonvulsant carbamazepine is not suitable as monotherapy to stabilize mood, but does have anti-aggressive properties useful for treating rage attacks.[8]

Lamotrigine is a newer anticonvulsant that significantly improves depression in BD.[4] It is not recommended for mania but can be useful for rapid cycling (see below). However, side effects proscribe its use for children under 16 years (Child and Adolescent Bipolar Foundation, 2002).

Lamotrigine has a low switching rate (conversion of depression to manic phases), but potentially serious adverse effects.[55] It causes skin rash in approximately 15 percent of patients or more severe dermatological reactions, including the potentially fatal Stevens-Johnson syndrome (in 0.1 percent of patients).[54] These risks can be decreased by titrating the dose. When lamotrigine is added to valproate, a lower starting dose and slower titration are necessary because valproate can increase serum lamotrigine levels.[55]

Most BD patients require combinations of mood stabilizers to remain in remission. There is evidence that lithium, valproate, and carbamazepine lose efficacy over time and that this tendency is reduced when they are combined.[55] In rapidly cycling patients with frequent depressive episodes, triiodothyronine or possibly other thyroid hormones can augment lithium and the other mood stabilizers.[59] Clearly no existing medication or combination provides exceptional benefit without side effects.

Atypical Antipsychotics

For BD patients refractory to the recognized mood stabilizers, or for those with psychosis, anecdotal experience suggests combining a mood stabilizer with an atypical antipsychotic. These drugs (especially olanzapine and risperidone) are occasionally prescribed for manic states, particularly when rapid control is needed or when delusions or hallucinations are involved.

Olanzapine was tested in a large, still unpublished, eight-week randomized trial with bipolar I patients.[55,60] It was found significantly more effective than placebo for the depression of BD, and even more effective when used in combination with the antidepressant fluoxetine. Olanzapine can cause depression, somnolence, and weight gain.[4]

Risperidone has some evidence supporting its use against psychosis in BD.[55] It can also cause weight gain that averages more than five pounds in three weeks.[4]

When depression of BD is accompanied by marked anxiety or insomnia, a short course of a high potency benzodiazepine such as lorazepam or clonazepam may be helpful.[50]

Antidepressants

Antidepressants are not first-line treatment for the depression of BD or the disorder as a whole. Although they are effective for the depression of BD, they are less so than for unipolar depression and can cause switching to mania or trigger rapid cycling.[50] These risks are greater with tricyclic antidepressants (TCAs) than with selective serotonin reuptake inhibitors (SSRIs). In a review of bipolar trials the rate of switching to mania was 11.2 percent with TCAs, 3.7 percent with SSRIs, and 4.2 percent with placebo (SSRIs versus TCAs, $p < 0.01$).[50] Therefore, TCAs should be completely avoided and antidepressants as a class provide only limited adjunctive potential.[50] SSRIs such as bupoprion or venlaxafine may be indicated when severe depression does not respond to a mood stabilizer regimen.

Some antidepressants can also interact adversely with lithium. For example, TCAs with lithium cause increased incidence of tremor and myoclonus.[12] A serious interaction of lithium with fluoxetine has been reported in which lithium blood levels increased and neurotoxicity occurred after fluoxetine was added to a stable lithium regimen.[61] Fluoxetine may also increase the levels of valproate.[62] Also, when used with carbamazepine, fluoxetine was linked to moderate-to-severe parkinsonian symptoms.[63]

Sertraline was reported to increase levels of the anticonvulsant lamotrigine (see above).[64] Conversely, valproate may increase TCA levels, while carbamazepine can induce their metabolism.[12]

Failure to respond to one class of antidepressants should lead to trial of another class. Monoamine oxidase inhibitors have some effectiveness, but dietary restrictions and safety issues limit their clinical utility.[50]

Other Pharmaceuticals

Benzodiazepines are also frequently used in combination with mood stabilizers. These are not effective as monotherapy for BD, but can be helpful in the management of agitation, anxiety, and insomnia associated with mania and depression.[12] Used in combination with lithium, clonazepam caused neurotoxicity, specifically ataxia and dysarthria, in five cases.[65]

The calcium channel blockers (verapamil, nimodipine, isradipine) have received attention as potential mood stabilizers for treating acute mania, ultra-rapid cycling, and recurrent depression.[8] Verapamil can cause sexual dysfunction and has possible neurotoxicity when used in combination with lithium or carbamazepine.[54]

The complex nature of BD and the apparent wide array of pharmacotherapeutic options have spawned complex flowcharts and algorithms to facilitate treatment choices. However, in a 2000 conference a consensus was developed that greatly simplified the approach to most cases.[66] Following a survey of allopathic experts, an extensive treatise recommended mood stabilizers be used during all phases of treatment. If monotherapy fails, combination therapy should be tried. For severe depression standard antidepressants may be employed. For rapid cycling, whether from depression or mania, valproate monotherapy is recommended. Thyroid support is endorsed, on a limited basis. While impressive for its intended scope, this document is notable for its lack of attention to non-allopathic options for BD.

Electroconvulsive Therapy (ECT) for Resistant Cases?

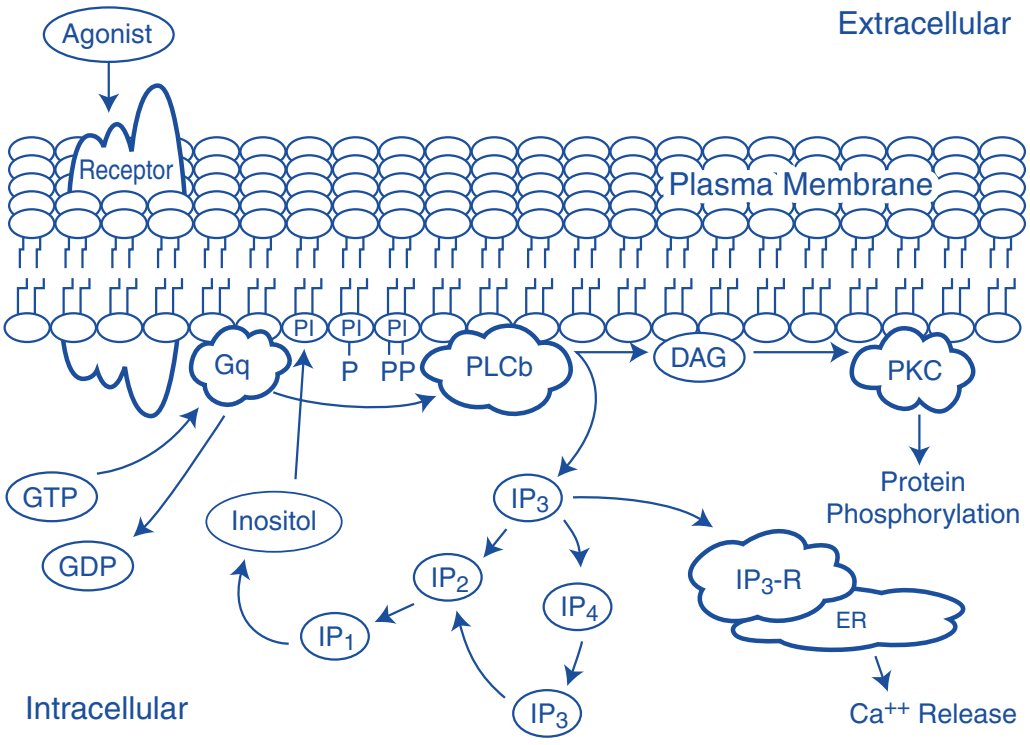
For treatment-resistant depression of BD, particularly with retardation and delusions, electroconvulsive therapy (ECT) is often recommended.[50] A large body of data seemingly supports its effectiveness for adults as well as adolescents.[67] ECT causes amnesia in fully half the patients treated.[67,68] This includes both transient retrograde amnesia, involving rapid forgetting of newly learned information, and retrograde amnesia, involving loss of memory for information learned before treatment. The latter can be persistent or permanent in adults and adolescents.[69] In some places ECT is not allowed on children under age 16 years.

If ECT is aggressive therapy, then TMS (transcranial magnetic stimulation) is subtle. TMS uses alternating magnetic fields to induce electrical currents in cortical tissue. Depending on the stimulation parameters, cortical excitability may be increased or decreased. TMS has been used primarily to treat major depression, and a recent meta-analysis strongly indicates repetitive TMS (rTMS) has antidepressant properties (reviewed in Burt et al[70]). To date, two studies on patients with mania conducted by the same group are contradictory.[70] A single published case history exists of a patient with euphoric mania who experienced marked improvement during monotherapy with rTMS at the right prefrontal cortex.[71]

Mood Stabilization at the Cell Membrane Level

Protein receptors for neurotransmitters and myriad other messenger substances are embedded in the outermost cell membranes of neurons (and often their support cells or glia). Once bound by a diffusible messenger (agonist), the receptor protein undergoes a shape change affecting other proteins nearby. An interconnected web of membrane protein complexes transduces the original signal into changes in activity, first within the membrane, then the entire cell. These are the signal transduction processes, which the cumulative evidence suggests are deranged in bipolar disorder.

Figure 1. *The Cell Membrane and Signal Transduction*



Activation of the receptor by an agonist results in the exchange of GDP for GTP on the coupled G-protein (Gq). Thus activated, Gq stimulates phospholipase C-B (PLC-B) to hydrolyze phosphoinositides in the plasma membrane. Hydrolysis of phosphatidylinositol 4,5-bisphosphate (PIP_2) forms diacylglycerol (DAG), which activates protein kinase C (PKC), and inositol trisphosphate (IP_3), which activates the IP_3 receptor (IP_3-R) on the endoplasmic reticulum (ER) to release calcium. The IP_3 is phosphorylated to form inositol tetrakisphosphate (IP_4) or is dephosphorylated to inositol bisphosphate (IP_2), which is sequentially dephosphorylated to form inositol monophosphate (IP_1) and free inositol. Phosphatidylinositol (PI) is synthesized from inositol and is sequentially phosphorylated to form phosphatidylinositol phosphate (PIP) and PIP_2.

Gq=G protein; GDP=guanine diphosphate; GTP=guanine triphosphate; PLC=Phospholipase C; DAG=diacylglycerol; PKC=protein kinase C; PI=phosphatidylinositol; PIP and PIPP=phosphatidylinositol phosphates; IP_1-4=various inositol phosphates.

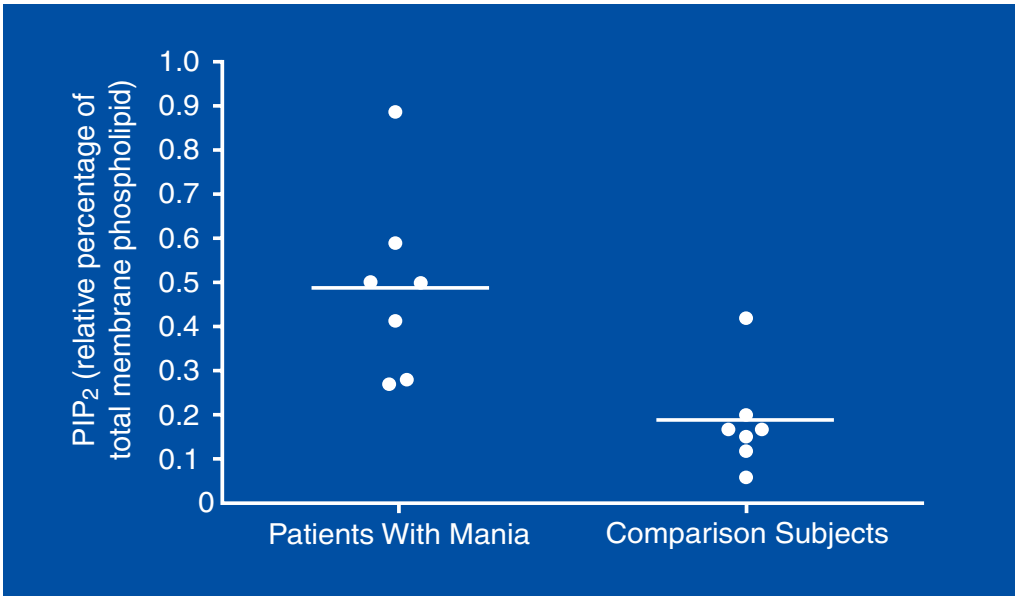
Adapted from: Pacheco MA, Jope RS. Phosphoinositide signaling in human brain. Progress in Neurobiol 1996;50:255-273.

Signal Transduction Abnormalities

The first linkage of a neurotransmitter receptor is usually with G proteins – three-isoform complexes assembled from at least 37 different isoforms. The multiplicity of isoforms allows for a multiplicity of graded responses of the G protein system. There is good evidence G protein pathways are abnormally overactivated in BD.[23]

Downstream from the G proteins, but still associated with the membrane, are the adenyl cyclase enzymes, also assembled from multiple

Figure 2a. *Phosphatidylinositol-bisphosphate (PIP2) in Membranes of Platelets Drawn from Manic, Unmedicated BD Patients*[77]



isoforms. The product of adenyl cyclase is cyclic AMP (cAMP), which quickly degrades in postmortem brain so it cannot be measured. cAMP-dependent protein kinase, a protein/enzyme complex activated once cAMP binds to it, is measured instead. In the BD brain this complex apparently is more sensitive to binding activation by cAMP.[72]

Another membrane-associated signal transduction system is protein kinase C (PKC). Inactivated PKC dwells in the water phase (cytosol) and then, on activation, translocates from the cytosol to the membrane. PKC membrane-associated activity has been measured significantly higher in the frontal cortex of BD patients.[73] Lithium can inhibit the PKC translocation process.[74]

The membrane phosphatidylinositol (PI) protein complex is a particularly important signal transduction pathway.[75] It is activated by multiple receptor systems, some of which are coupled to regulatory G proteins on the interior membrane face. Thus, by being coupled to G protein, the serotoninergic 5-HT2, alpha1-adrenergic, and muscarinic cholinergic receptors can activate the PI complex and subsequently the entire cell (Figure 1).

Activation of the complicated PI pathway begins when membrane PI phospholipid molecules are transformed by membrane enzymes into phosphatidylinositol 4,5- bisphosphate (PIP2), then split by a membrane phospholipase enzyme (phospholipase C) into inositol 1,4,5-trisphosphate (IP3) and diacylglycerol (DAG).[75] DAG diffuses out of the membrane to activate PKC proteins in the cytosol. IP3 also diffuses out to initiate calcium release into the cytosol. Many key cellular functions are regulated by these two pathways.

Later, IP3 is recycled to regenerate membrane PI.[75] First it is degraded to IP2 (inositol bisphosphate) then to IP (inositol monophosphate), which is then converted by the enzyme inositol monophosphatase into free inositol (myo-inositol). This is a precursor for re-synthesis of PI in the membrane.

Circulating blood platelets, with their content of serotonin and other neurotransmitters, are thought to be useful as accessible experimental "models" of certain neuronal activities.[76] In 1993, analysis of platelets drawn from unmedicated, manic BD patients disclosed abnormally high levels of PIP2 in their membranes.[77] This suggested the PI signal transduction system might be overactivated in BD. By 2001, a similar analysis of platelets from unmedicated, depressed BD patients found they also had abnormally high PIP2[76] (compare Figure 2a with Figure 2b). These findings further support hyperactivity of the membrane

PI signal transduction pathway as causal to BD. The platelet findings concur with reports of increased intracellular Ca2+ release in BD patients in various mood states.[78,79]

Lithium, Valproate Partially "Fix" Signal Transduction

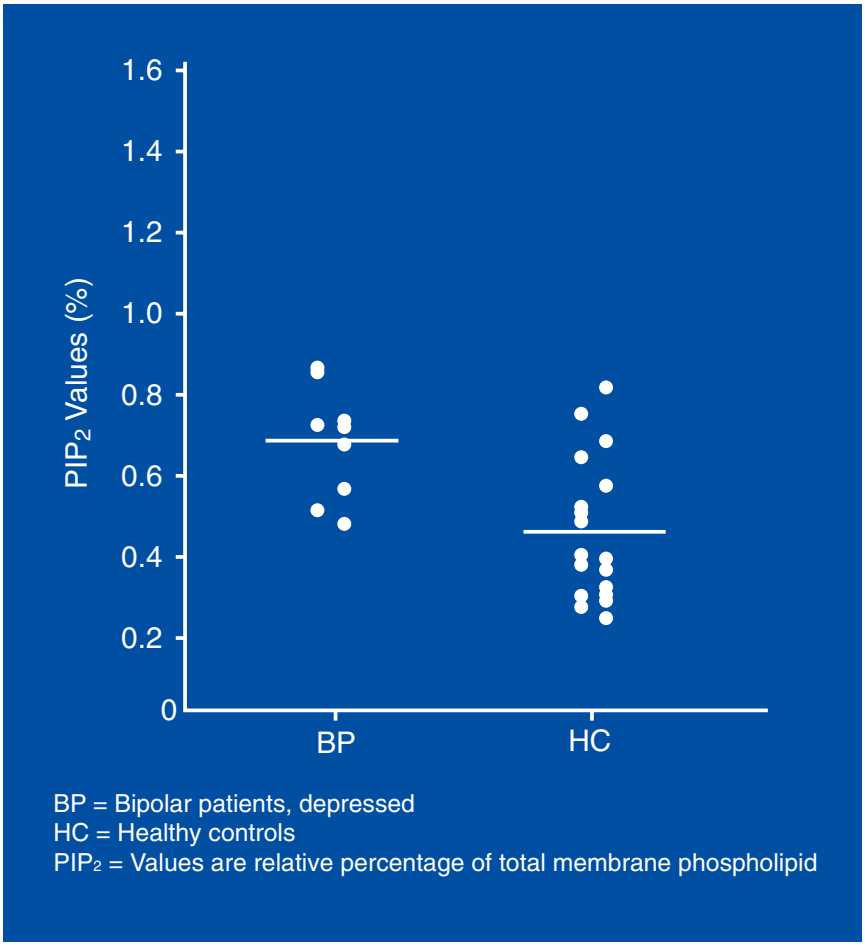
In a study on platelet calcium release,[80] a total of 73 BD patients with mania, BD patients with depression, treated euthymic BD patients, unipolar depressive patients, and controls were assessed for baseline platelet intracellular calcium, then for intracellular calcium increase following platelet stimulation. The manic BD patients showed significantly higher baseline platelet calcium compared with the other groups. On stimulation, both the manic BD patients and depressed BD patients showed greater buildup of free platelet calcium than did the control and MDD patients. Euthymic BD patients who had been treated with lithium, antidepressants, or ECT were not significantly higher in platelet calcium than were the controls at baseline, and did not show abnormally enhanced calcium sensitivity on stimulation.

Thus, substantial available evidence suggests that four key membrane-based signal transduction pathways could be overactive or oversensitive to receptor stimulation in BD – the G protein system, adenyl cyclase, PKC, and PI system. Furthermore, the main molecular targets of both valproate and lithium are very likely the post-receptor signal transduction systems.[14]

Recent mechanistic research on lithium has focused on the PI pathway. Excessive activity of this pathway could cause abnormally elevated release of neurotransmitters from neurons, including serotonin, dopamine, and norepinephrine. This could help reconcile some of the anomalous observations on these transmitters in BD patients. Blocking the inositol monophosphatase enzyme by lithium could inhibit the supposedly overactive PI cycle. Lithium therapy was found to lower the platelet PIP2 levels of manic patients after three weeks.[81] Platelet membrane analyses also showed elevated PKC activity in both manic[82] and depressive[83] BD patients. Here also, lithium therapy for mania lowered the platelet PKC activity.[82]

Like lithium, valproate is a first-line mood stabilizer. Valproate is likely having its effect by blocking PKC.[84] Experimentally, lithium and valproate produce a synergistic inhibition of the

Figure 2b. *Phosphatidylinositol-bisphosphate (PIP2) in Membranes of Platelets Drawn from Depressed, Unmedicated BD Patients*[76]



PI system, consistent with each agent inhibiting a different branch of the PI-dependent signal transduction cascade. This may be the membrane-level basis for the superior efficacy of lithium-valproate combination therapy in BD.

Bad Genes: Monophosphatases, Phospholipases, Kinases?

Final proof the PI signal transduction is the operative dysfunctional mechanism in BD awaits studies in which agents that specifically block membrane inositol-metabolizing enzymes also cause linked clinical benefit.[79,85] The late David Horrobin suggested the mood cycling so characteristic of BD, and lithium's inhibition of both mania and depression, could be more satisfactorily explained by another signal transduction mechanism.[14] Chang and colleagues found lithium was a powerful inhibitor of a phospholipase A enzyme (PLA2) which also has profound involvement in signal transduction.[86] Horrobin noticed that this inhibition occurs in the brain, and that it occurs at lithium concentrations lower than for any of lithium's other known biochemical targets.[14]

If Horrobin's hypothesis is proven correct – that PLA2 is the central mechanism for lithium's activity – the cycling mechanisms characteristic of BD could be rationalized. In healthy individuals PLA2 normally functions to free long-chain fatty acids (LCFAs) such as arachidonic acid (AA) and eicosapentaenoic acid (EPA) from their membrane phospholipid anchors. Both of these are eicosanoid-prostaglandin (PG) precursors.[75] Therefore, if PLA2 activity is abnormally elevated in BD, there would be prostaglandin overactivity. Once the relevant membrane stores become depleted of LCFAs, as can occur from poor diet or other adverse life influences, PG production could collapse, resulting in a "flip" from excessively high PG production to excessively low PG production. If the LCFAs and their derivatives are important in regulating mood, this would explain the mood cycling of BD.

As early as 1989, Hibbeln and colleagues had garnered substantial evidence that PLA2 overactivity could be operative in bipolar disorder.[87] While noting the norepinephrine and serotonin imbalances hypotheses were yet unproven, they linked PLA2 overactivity to possible norepinephrine insufficiency. PLA2 can down-regulate tyrosine hydroxylase, the rate-limiting enzyme for norepinephrine and other catecholamine synthesis.[88] Hibbeln and colleagues also linked PLA2 to impaired reuptake and receptor action of serotonin.[87,89]

Evidence of the enhanced production of prostaglandin E1 (PGE1) (an omega-6 AA derivative) in mania, and its lowered production in depression,[90] is consistent with Horrobin's hypothesis. Lithium's ability to inhibit PLA2 (at low concentrations comfortably within its therapeutic range [>80% inhibition at 0.06 millimolar lithium]) then causes it to block both the excessive PG release phase ("mania") and the insufficient PG release phase ("depression").

Horrobin further extended the PLA2 overactivity hypothesis to rationalize the efficacy of neurotransmitter antagonists in mania.[14] Much of the physiological drive that maintains PLA2 activity comes via the occupation of serotoninergic (5HT2) and dopaminergic (D2) receptors. The blocking of PLA2 by lithium, and/or the indirect reduction of PLA2 drive by 5HT2 or D2 blockade, would both help control the mania. Considering that the omega-3 LCFA counterbalance the omega-6 profile of the membrane, this hypothesis can be accorded further clinical relevance.

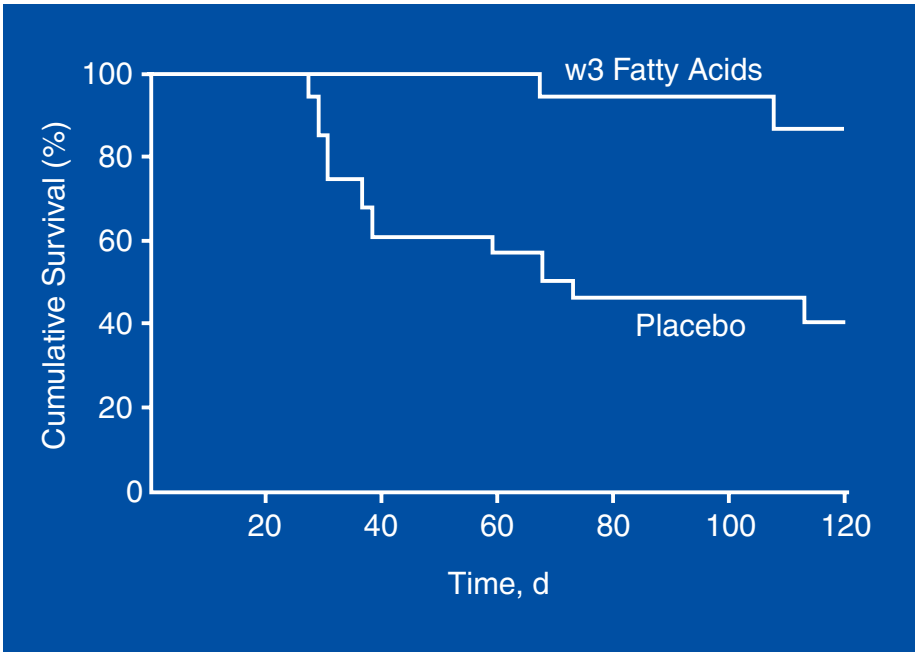
Horrobin indicted the gene (or genes) controlling PLA2 as the main candidate "psychosis" gene.[14] Long a supporter of the continuum perspective on affective illness, he positioned the PLA2 gene(s) centrally in this continuum, as common to BD, SCZ, and MDD. Interactions of this central gene with others more specific to the other disorders would then account for the symptom continuum and many of the comorbidities as well. Only time and further research will verify whether PLA2 or genes for some other membrane signal transduction enzymes (phosphatases? kinases?) eventually take the central position as the "villain" in BD.

Omega-3 EPA and DHA Nutrients Stabilize Mood

The omega-3 long-chain fatty acids EPA and docosahexaenoic acid (DHA) have emerged as effective mood stabilizers in BD. A Harvard-based, U.S-European collaborative trial conducted on BD patients with EPA+DHA as fish oil versus placebo resulted in a significantly high rate of response to treatment.[91] Although the patient sample was relatively small, the study was otherwise well-designed. It demonstrated significantly longer remission due to EPA+DHA, and significant improvements over placebo on a variety of outcome measures. Conducted by Stoll and collaborators, this was a four-month, parallel group, double-blind trial of 30 male and female unstable BD outpatients, ages 18-65, who had exhibited at least one manic or hypomanic episode within the previous year. In addition, 40 percent of the subjects had experienced rapid cycling symptoms during this period. Subjects were maintained on whatever medications they were receiving at study entry, then randomly assigned to either placebo (olive oil ethyl esters) or concentrated omega-3 fatty acid capsules standardized by the Fish Oil Materials Program (a joint research project of the U.S. National Institutes of Health and the Marine Fisheries Service). Each capsule provided 440 mg EPA and 240 mg DHA; the dose was seven capsules twice daily for a total of 6.2 g EPA and 3.4 g DHA daily.

The main outcome measure in the Stoll study was the duration of time to exit the study because of BD symptoms of sufficient severity to warrant change in medication.[91] The two blinded principal investigators collaborated with each patient to make this decision. This meant that the longer the patient stayed in the study, the better was the treatment efficacy (hence the Kaplan-Meier "survival" plots). Secondary outcome measures were the results on several rating scales: the Young Mania Rating Scale (YMRS), the Hamilton Rating Scale for Depression (HAM), the Clinical Global Impression (CGI), and the Global Assessment Scale (GAS). Of the EPA+DHA group, 9/14 patients responded to treatment versus 3/16 in the placebo group (p=0.02). The duration of remission was also significantly greater for the EPA+DHA group over the placebo group, as illustrated in Figure 3 (p=0.002). The EPA+DHA group also significantly improved over the placebo group on the HAM, CGI, and GAS scales. The most common adverse effect was mild gastrointestinal distress with generally loose stools. This occurred equally in both groups and no other significant adverse effects occurred.

Figure 3. *Double-blind Trial: Kaplan-Meier Cumulative Recurrence-free Interval for the Omega-3 Group versus the Placebo (Olive Oil) Group. "Survival" on the y-axis Indicates Continued Remission.*[91]



Flaxseed Oil versus Fish Oil

Stoll and colleagues also reported on an earlier open-label study of flaxseed oil administered to 22 BD patients.[54] Flaxseed oil is a potent source of alpha-linolenic acid (ALA, C18:3), a shorter-chain, omega-3 fatty acid not prevalent in human cell membranes *in vivo*. The dose of flaxseed oil was unspecified but implied to be one tablespoon daily (providing 7 g ALA). Initially, a majority of the patients appeared to benefit, but subsequently several cases of mania and hypomania emerged that were attributable to the flaxseed oil.

Earlier, Dr. Donald Rudin, a pioneer in omega-3 clinical application, reported similar findings from case histories.[92,93] Rudin observed that flaxseed oil seemed to have a narrow therapeutic window and often caused adverse effects with extended application. The physiological role of ALA in cell membranes, if any, remains unknown and its presence in membranes is limited. EPA and DHA are the representative omega-3 fatty acids in human membranes.[94,95]

The possible mechanisms by which EPA and DHA could improve mood in BD include:

- EPA and DHA are intrinsic to the molecular structure of the phospholipids of cell membranes, making up the "tails" of the molecule.
- The membrane's phospholipids are integral to its signal transduction mechanisms.[96] The fatty acid tails are essential to their roles in modulating the functioning of proteins in the membrane.
- EPA and DHA lend fluidity to cell membranes.[96] Due to the multiple double-bonds in their structure, when incorporated in membrane phospholipids they produce a more loosely packed and "fluid" membrane matrix. They also have stereospecific functional interactions with membrane enzymes, receptors, and other proteins.
- EPA and DHA can inhibit the PKC signal transduction enzyme complex, in a manner similar to valproate.[54,97]
- EPA and DHA can block calcium influx into the cell through the L-type calcium channel, similar to the calcium channel blockers verapamil or nimodipine.[98]

Other Nutrients Beneficial in Bipolar Disorder

Since the 1950s[99] and perhaps even earlier,[100] nutritional supplements have been used in BD. However, BD seems underinvestigated when compared with major depression or even schizophrenia. Investigations that involved BD subjects are reviewed in this section.

Phospholipids

Phospholipids are the primary molecular building blocks of cell membranes. As diagrammed in Figure 4, the most common membrane phospholipid PC typically consist of a headgroup, a middle piece, and two tails. The middle piece is by definition derived from glycerol. The headgroup contains a phosphoryl group in combination with choline, but ethanolamine, serine, or inositol can be inserted to yield phosphatidyl -ethanolamine (PE), -serine (PS), or -inositol, respectively. The headgroup endows the phospholipid with a unique physico-chemical profile.

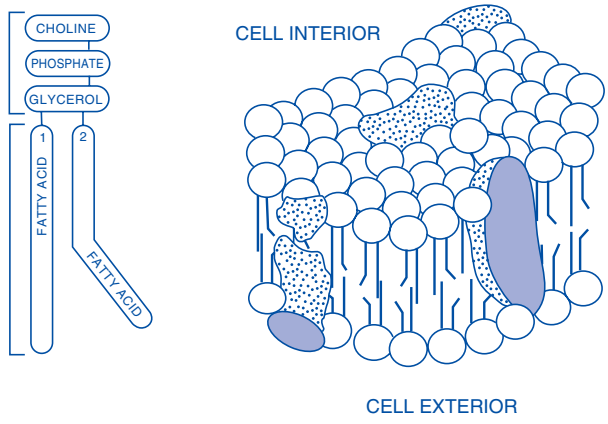
The tails are esterified fatty acids, and the extent of unsaturation confers degrees of fluidity on the membrane, although their stereospecific binding to other membrane molecules is also important. Normally, the fatty acid most employed to lend fluidity to cell membranes is DHA with its six double bonds, but EPA with five is also effective. Phospholipids are "parent" molecules that appropriately position fatty acids in the membrane for their functional roles as precursors of eicosanoids (prostaglandins) and signal transduction effector molecules.[53,96]

Lecithin (mixed phospholipid) preparations can benefit mania. In 1980 Cohen and associates reported administering a lecithin with 90-percent PC as a food supplement, at a dose of 15-30 g daily, to four manic BD patients also receiving lithium and/or neuroleptics.[101] All showed "marked improvement." Manic symptoms reappeared in three of the four patients after the lecithin/PC was discontinued. Subsequently, in a small double-blind trial, Cohen et al found lecithin/PC significantly improved mania in five of six patients.[102]

Schreier reported a case history of an adolescent BD patient who was successfully maintained on lecithin/90-percent PC (15-23 g daily) for more than two years.[103] The manic-psychotic patient – formerly highly agitated and aggressive – remained in remission after being removed from lithium and maintained on PC alone.

More than three decades ago, researchers posited the membrane hypothesis of bipolar disorder (and schizophrenia), wherein patients responsive to lithium were thought to have functional membrane abnormalities.[104] Later the putative mechanism(s) were further localized to membrane signal transduction.[105] PC's role as the major quantitative membrane phospholipid is consistent with this mechanistic rationale and its anti-manic benefits.[53]

Figure 4. *Basic Molecular Organization of a Cell Membrane with Schematic of Phosphatidylcholine. From Alberts et al (editors), Molecular Biology of the Cell.*[96]



Antioxidants

Bipolar disorder patients may have impaired antioxidant defenses. In 1955 Altschule reaffirmed earlier occasional case reports of low blood glutathione in "manic-depressive" patients.[106] A 2002 study reported elevated malondialdehyde, a lipid peroxidation end-product, in blood from BD patients.[107] Braverman and Pfeiffer[100] reported occasional positive results from supplementation with a sulfur-containing antioxidant.

The importance of ascorbic acid (vitamin C, ascorbate) was recognized in psychiatry more than half a century ago when Abram Hoffer, MD, and Humphrey Osmond, MD, established it as a pivotal nutrient for schizophrenia.[108] In 1963, Milner conducted a double-blind trial on 40 institutionalized psychiatric patients (including four manic-depressives), with 1 g vitamin C daily versus placebo for three weeks.[109] The BD patients on vitamin C experienced significant symptomatic improvement.

In 1981 Naylor and Smith conducted a double-blind, placebo-controlled, crossover trial of vitamin C (3 g daily of an oral effervescent aqueous preparation) on BD patients.[110] The trial lasted just two days and the patients were assessed hourly using global scales for mania and depression. Both the manic and the depressive BD patients reported significant improvements 3-4 hours following ascorbate intake. Subsequently, in a small double-blind trial Naylor and associates tested ascorbate (4 g daily) in combination with ethylene diamine tetra-acetic acid (EDTA), and did not see added benefit against mania or depression.[111]

Vitamin E was reported ineffective against BD after a 1971 study.[112] However, the dose was relatively low (150 mg daily) and only two patients were involved. Deficiency of this vitamin is linked to impaired neurological function,[113] so future study with higher doses would seem justified.

B Vitamins

Vitamins B3, B6, B12, and folic acid have all proven beneficial in the treatment of mental disorders when prescribed at intakes beyond those typical of mixed B-vitamin formulations.

Folate deficiency, the most common nutrient deficiency, may be found in over one-quarter of hospitalized psychiatric patients,[114] and is often associated with depressive symptomatology.[114,115] Lithium carbonate can cause a folate deficiency.[114]

Alterations in the brain concentrations or regional distributions of serotonin (5-hydroxytryptamine) and norepinephrine are perhaps involved in the initiation or triggering of BD episodes,[105] and folate deficiency has been associated with poor serotonin status.[114] Folate is an essential coenzyme for the biosynthesis of tetrahydrobiopterin (BH4), which is important for the biosynthesis of both norepinephrine and serotonin; BH4 metabolism may be abnormal in BD.[116]

Folate is also important in methylation – the conversion of single carbon units into methyl (CH3—) groups that help regulate many pathways. In one study involving 11 manic BD patients, methylation activity was significantly reduced in the red cell membrane, which is a valid indicator of systemic methylation capacity.[117] The nutrient s-adenosylmethionine (SAMe) could prove effective to restore methylation in BD patients, but can cause switching to mania.[118] High-dose folate supplementation may well prove an effective substitute.

Vitamin B12 deficiency has been linked to psychosis and mania.[105,119] Folate metabolism is closely tied with vitamin B12 metabolism and, since folate sufficiency can sometimes mask the symptoms of B12 deficiency, it may be prudent to prescribe the two together.

Amino Acids

Several amino acids are precursors to brain neurotransmitters.[120] The most publicized is tryptophan, a dietarily essential amino acid first metabolized to serotonin and then to melatonin. Tryptophan uptake is apparently not regulated by the blood-brain barrier, and meal-to-meal fluctuations in blood tryptophan levels are linked to clinically significant fluctuations in brain functions that rely on serotonin.[120] A similar phenomenon is observed with tyrosine, the precursor for the catecholamine transmitters dopamine, norepinephrine, and epinephrine.[120] Early theories of BD etiology envisioned abnormalities in brain serotonin and/or catecholamine activity that led to clinical exploration of free amino acids for BD therapy.[121,122]

L-Tryptophan

Oral dosing with L-tryptophan has been found to benefit BD. In 1974 a very small, five-patient, short-term, crossover, double-blind study suggested 6 g oral, free-form tryptophan daily benefited mania in BD patients.[123] Another small, 10-patient, double-blind study that same year reported BD benefit from an average dose of 9.6 g tryptophan daily.[124] In 1985, a slightly larger (24 patients), short-term, crossover, double-blind, placebo-controlled study with 12 g tryptophan daily showed a statistical trend in favor of benefit ($p<0.10$).[125] In the interim (1978), one small (10-patient) study failed to show benefit.[126]

Tryptophan may potentiate the action of lithium. In a double-blind trial of nine patients, 3 g tryptophan three times daily combined with lithium produced significantly greater improvement over lithium alone.[127] In a published case history, tryptophan was reported to improve BD II in a patient who had failed to respond to lithium.[128]

There are significant barriers to using tryptophan as an oral supplement, however. First, it may not work reliably against BD, the effective dose range potentially being higher than for unipolar depression, and at this level many patients still may not benefit.[129] Second, because its blood levels are not carefully regulated in the brain, at relatively high concentrations it can drive enzyme reactions that can generate toxic metabolites. In this case a classic orthomolecular substrate concentration drives an enzymatic catalysis that operates against the patient. Werbach in his "Nutritional Influences on Illness"[130] warns tryptophan can have the following potentially adverse actions:

- Tryptophan breakdown products may cause auto-antibody production.

- High doses often cause nausea.

- Tryptophan supplementation may promote bladder cancer in patients deficient in vitamin B6.

- Tryptophan may reduce the efficacy of morphine analgesia.

- Poorly manufactured tryptophan may cause potentially lethal eosinophilia-myalgia syndrome.

Certain groups should avoid large, chronic doses, including children and individuals with achlorhydria, adrenal insufficiency, asthma, cancer, diabetes, lupus erythrematosus, or scleroderma. Pregnant women are advised to avoid tryptophan entirely.

Even the most experienced orthomolecular practitioners recommend that oral dosing with free form L-tryptophan is best performed under a physician's close management.[100]

5-Hydroxytryptophan (5-HTP)

5-HTP, a metabolite of tryptophan, is the immediate metabolic precursor of serotonin and has been touted as a replacement for tryptophan. Several double-blind trials and some open trials indicate 5-HTP is an effective antidepressant, including in BD, with more than half the patients showing very good to moderate improvement.[131,132] Treatment-resistant patients, some with long disease duration, also respond to this nutrient; however, few of the trials lasted longer than one month. To adequately establish 5-HTP's longer-term efficacy controlled trials of longer duration are needed.

The safety of 5-HTP as a dietary supplement for BP is unclear. One problem is that it can induce mania in depressed patients.[133] When taken with SSRI inhibitors, by increasing serotonin levels, it can cause serotonin syndrome – agitation, confusion, delirium, tachycardia, diaphoresis, and blood pressure fluctuations.[134] The gastrointestinal adverse effects of 5-HTP – vomiting, nausea, diarrhea – can be ameliorated by titrating the dosage upward from 50 mg daily.[134]

5-HTP is more bioavailable to the brain than its precursor tryptophan, and is likely more manageable for adverse effects, but probably should also be administered under professional management.

Multivitamin-Minerals – Other Nutrient Combinations

A broad-spectrum dietary supplement was developed by a group in Canada, based on treatment of mood problems in livestock subjected to stress. A University of Calgary group led by Kaplan administered it to a case series of BD patients for six months.[135] The 32-capsule daily dose provided B vitamins at many multiples of the RDA, a full range of essential minerals mostly as chelates (but not lithium), and a "proprietary blend"in unspecified amounts of miscellaneous other nutrients (for a listing refer to the Appendix in Kaplan et al.[135]) After two weeks, overall marked benefit was noted, with significant improvements on rating scales for depression, mania, and general psychiatric status. Of the 11 patients who completed this open trial, seven were judged responsive to the treatment. The number of pre-trial, psychoactive medications was reduced by more than half (from a mean of 2.7 to 1.0). In two cases the supplement fully replaced psychoactive medications and the patients remained well. An admitted shortcoming of this trial is that 10 of the 11 patients were men.

In a commentary that accompanied this paper, Charles Popper, MD, from the Dept. of Psychiatry at Harvard Medical School explained the history of this supplement.[136] An animal nutrition specialist David Hardy brought the approach to Anthony Stephan, a parent of two bipolar children who then added similar nutrients to the children's diet. The children stabilized clinically and were still off psychiatric medication after five years, as of publication in 2001.[136] According to Popper, Hardy and Stephan claimed to have since

worked with over 2,500 psychiatric patients.

Popper has also discussed 23 patients who he had placed on supplement combinations similar to the Hardy-Stephan formulation.[136] He reported 20 of them showed benefit, and that of 15 who came to him on medications 11 had since become stable for 6-9 months without medications.

In 2003 Simmons reported on 19 BD patients to whom he administered the formulation.[137] He observed that 12 of the 19 patients showed marked clinical improvement, three showed moderate improvement, and one showed mild improvement. Thirteen patients were able to completely discontinue psychiatric medications over a period of 3-10 weeks; after 13 months 11 of the 19 remained by preference on the formulation alone without medication.

Rational Bases for Integrative BD Management

Bipolar disorder is a challenging illness to treat. Much progress has been made toward understanding its pathophysiology and allopathic options have diversified. A strategy for its effective integrative management is beginning to emerge.

Lifestyle Changes are Essential

Cigarette smoking is a significant contributor to depression. Central to the effect of nicotine is the stimulation of adrenal stress hormones, including cortisol.[41] Alcohol is also a brain depressant. Like nicotine, alcohol increases adrenal hormone output, interferes with many brain cell functions, disrupts normal sleep cycles, and contributes to hypoglycemia. The resultant sugar craving initiates a vicious cycle of sugar overconsumption that ultimately exacerbates the hypoglycemia.[41]

People feeling depressed or anxious tend to be especially sensitive to caffeine. Murray summarized several studies that indicate a person who consumes more caffeine has a higher risk for depression, and that a depressed patient tends to consume fairly high amounts of caffeine (more than 700 mg daily).[41] Bipolar subjects tend to abuse caffeine as a kind of self-medication.[138]

The combination of caffeine and refined sugar appears to be worse than either consumed alone. Murray reviewed studies that found an association between this combination and depression, among them two double-blind trials.[41] He advocated that people with depression avoid caffeine completely.

Exercise may be the most powerful antidepressant available. Various community and clinical studies clearly indicate regular exercise decreases symptoms of depression, anxiety, insomnia, and malaise.[139] These benefits are perhaps related to the release of endorphins in the brain. Murray referred to more than 100 studies establishing regular exercise as a powerful antidepressant.[41]

Dietary Revision

Like other organs, the brain is vulnerable to functional impairment from nutrient deficiencies or imbalances. Simply removing refined carbohydrates from the diet will improve hypoglycemia. Depressed BD subjects may be relatively insulin resistant, while manic subjects may be hypersensitive to insulin.[140] For the most meaningful hypoglycemia-dysglycemia assessment, Murray recommended blood insulin be measured along with glucose with a glucose-insulin tolerance test.[41]

Omega-3 fatty acids (long-chain EPA+DHA) show great promise to benefit BD patients, based on the double-blind trial discussed above.[54] The dose used was high – almost 10 g EPA+DHA – making increased intake via foods almost mandatory.[90] The "typical" U.S. and Western European diet, however, is largely depleted of omega-3 fatty acids. The higher rates of major depression seen in many industrialized countries correlate with the relative paucity of dietary EPA+DHA.[54] The ratio of omega-6 to omega-3 intakes has increased from 2-4 early last century to more than 20 currently; some experts believe this accounts for the decade-by-decade increased incidence of major depression.[141]

Many integrative physicians monitor patient systemic fatty acid (FA) balance by testing

red cell membrane FA profiles and adjusting omega-3 intake recommendations if indicated. The omega-3 fatty acids are notoriously unstable without antioxidants and function best in cell membranes when antioxidant status is good. Therefore, a reasonable BD diet would emphasize antioxidant, anti-inflammatory foods. Care must be taken to avoid fish or other foods that may carry a high load of mercury or other pollutants.

Cooking without oil or using cooking oils that resist oxidation, such as extra virgin olive oil, should be emphasized. Bipolar patients should be careful of flaxseed oil, based on reports that continued intakes can trigger mania.[54,93] The conscientious BD patient will avoid refined foods with high burdens of sucrose, trans (hydrogenated) fats, poor nutrient content, and potentially toxic additives.

Dietary Supplementation Program

Supplementation of the diet with vitamins and other nutrients is indicated, both to support wellbeing and to protect against deficiencies that could contribute to disease exacerbation. Dietary supplements can also be used for overall normalization of health.

Vitamin C and other antioxidants play important roles in BD management. They modulate the types of prostaglandins and other eicosanoids that come from membrane fatty acids. This property directly supports membrane normalization as a basis for successful BD management.

Like all individuals with suboptimal health, BD patients are likely to benefit from dietary supplements that enhance intestinal detoxification and normalization, including probiotics and digestive enzymes. Known benefits from controlled trials make a strong case for generous supplementation of the daily diet with phospholipids, omega-3 fatty acids, a multiple vitamin with large amounts of the B vitamins, along with essential minerals and other antioxidant nutrients.

Health professionals must carefully consider the implications of prescribing SAMe, tryptophan, or 5-hydroxytryptophan to bipolar patients, as these come with questionable safety or other caveats to their use.

Cognitive and Other Psychotherapy

In addition to implementing the lifestyle and dietary modifications that can positively impact the frequency, severity, and duration of episodes, the BD patient is particularly advised to avoid emotional stress. Other mood stabilizing habits include stabilization of the home environment and daily routines, and avoidance of aggressive living, excessive goal seeking, and personal confrontations. Where these challenges become overwhelming, psychotherapy can be useful.

Cognitive-behavior therapy (CBT) has been shown to benefit BD in at least three controlled studies (reviewed in Otto et al[52]). CBT has at its core a step-by-step, goal-oriented, skills acquisition approach to deal with the disorder. CBT has at least five basic targets for treatment:[52]

1. Medication adherence. The need for improvement is striking, as adherence in BD often fails within the first few months of treatment. Patients may remember past manic episodes fondly and desire future episodes, or simply not be convinced of the need for preventive treatment. CBT elicits patient agreement that taking medication is necessary.

2. Early detection and intervention. CBT engages the patient and their family together with health professionals into a treatment contract, preferably in written form, complete with names and contact numbers for quick action as necessary.

3. Stress and lifestyle management. While activity monitoring and scheduling were early-established components of CBT, BD patients are also asked to add monitoring of the sleep-wake cycle and tracking of increases in activity that could herald a manic episode.

4. Treatment of comorbidity. High rates of psychiatric comorbidity typify BD patients – more than 40 percent demonstrate a comorbid anxiety disorder or substance abuse, for example. For comorbid anxiety disorder, which can significantly worsen prognosis, CBT appears to rival pharmacologic management.

5. Treatment of the depression of BD. CBT has a long history of success in the treatment of unipolar depression and is likely to be equally as effective in bipolar depression. Patients are initially instructed in a cognitive model of the interplay between thoughts, feelings, and behavior, followed by various emotional and problem-solving strategies, including assisting patients with emotional regulation, assertiveness, or comorbid anxiety management.

CBT has joined other forms of psychotherapy in providing promising adjunctive management of bipolar disorder.[8,52]

Therapeutic Parenting and Education

For children and adolescents with BD, regular therapy sessions with a licensed social worker, psychologist, or psychiatrist are often productive. Special educational needs will arise and should be dealt with, preferably by teamwork among the educational professionals, parents, and child. Cognitive therapy, interpersonal therapy, and multi-family support groups are also strongly recommended by the Child and Adolescent Bipolar Foundation (CABF).[8]

The CABF also educates parents on specific ways to help their offspring function with BD. There are techniques to calm children when they are symptomatic that can help prevent relapses. These include practicing and teaching the child relaxation techniques; restraint holds to contain rages; tailoring sound and lighting to assist the child with waking, relaxing, and falling asleep; reducing stress and arguments and helping the child anticipate stressful situations; positively engaging the child's creativity; and securing guns, medications, and other agents that could be used to inflict harm during a rage.

Conclusion

Bipolar disorder is potentially devastating to the individual and society. The social liability, lost productivity, financial costs, and the high rate of suicide combine to generate an urgent need for early diagnosis and management. Good data indicate the earlier treatment begins, and the fewer the episodes, the better the chance of establishing control over the illness.

Within just the past decade major advances have been made in the monitoring, treatment, pathophysiology, and management of bipolar disorder. Noninvasive brain imaging techniques combine with classic histopathology to define organic brain circuit alterations in this psychiatric disorder. Imaging also gives clues to abnormalities in membrane phospholipid metabolites that may hold the key to understanding BD.

Because bipolar disorder remains such a challenging condition to treat, dogmatic adherence to either a purely pharmaceutical approach or a purely "alternative" approach is not tenable. Patients with BD are so vulnerable to setbacks from environmental risk factors that effective management demands lifestyle and dietary reform and stress reduction. Pharmaceuticals still have an important role to play in BD, but preferably in conjunction with comprehensive dietary supplementation. Supplemental nutrients, while providing their own benefits, can also facilitate effective drug activity at lower dosages and help guard against the adverse effects associated with these potent pharmaceuticals.

The mineral lithium continues its prominence as the "gold standard" pharmacotherapy for BD. However, although it has good predictability, lithium has major adverse effects with a narrow therapeutic window, and a great many patients do not consistently benefit from it. Newer drugs are available, but all have frequent and troubling adverse effects.[9,55] As with innumerable other diseases and disorders, conventional allopathic management of BD remains woefully inadequate.

Recently the orthomolecular pioneer Jonathan Wright, MD, made a compelling case for lithium being a safe and well-tolerated neuroprotectant at low doses.[142] This introduces a worthwhile interim goal for integrative management in bipolar disorder: to use lithium to "take the edge off" while introducing nutrients and instituting lifestyle, dietary, and exercise reform. For most BD patients and their physicians this style of management would be relatively novel, but orthomolecular physicians have been following

this basic tenet for decades.

Supplementing with the omega-3 fatty acids with phospholipids, their parent molecules in cell membranes, along with the antioxidants that naturally protect cell membranes, could complement (conceivably even supplant) lithium's proven signal transduction actions. It seems probable that children, adolescents, pregnant women, or other sensitive populations expressing prodromal bipolar symptomatology would respond positively to such rational nutrient combinations. Only after these have been applied to maximum effectiveness would drugs have to be deployed. The next step would be the addition of low-dose lithium.

The power of nutrients to ameliorate such a severe illness as BD was dramatically expressed by the results of Hardy, Stephan, Popper, and Simmons with a multiple nutrient combination. As Popper philosophized:

"What if some psychiatric patients could be treated with inexpensive vitamins and minerals rather than expensive patented pharmaceuticals? Or what if some doses of psychiatric drugs could be reduced by the concurrent use of nutrients? The economic implications, for individual patients and for the pharmaceutical industry, are difficult to overlook.... Clinicians and researchers may need to rethink the traditional bias against nutritional supplementation as a potential treatment for psychiatric disorders."[136]

Management of bipolar disorder is at a turning point. The pathophysiology, risk factors, and treatment modalities are now sufficiently well clarified to enable a broader integrative approach to its clinical management. Additional research is always useful, but open-minded practitioners should gain courage from the ever-expanding array of tools available to fight this challenging disorder.

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