Bipolar Disorder as Cell Membrane Dysfunction

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FROM 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[1]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.

THIS AUTHOR ALSO NOTES:

[3]Since World War II, BD has been steadily worsening with earlier age of onset, greater intensity of symptoms, and development of drug resistance.[2]

Incidence in children is rising.

Lithium has been the foundational treatment, followed by valproate and other mood stabilizers, antidepressants, and anticonvulsants.

[3]Several single-nutrient and multinutrient supplements have also proven beneficial.[2]

[3]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.[2]

INTRODUCTION

[3]Bipolar disorder (BD; manic depressive illness) is a disorder of the brain characterized by extreme changes in mood, energy, thinking, and behavior.[2]

Prominent individuals with BD include Winston Churchill, Ernest Hemingway, Abraham Lincoln, Theodore Roosevelt, and Virginia Woolf.

BP is increasing, especially among children and adolescents, and is very difficult to manage.

[3]Bipolar disorder is a major cause of disability and premature death from suicide.[2]

[3]Inappropriate pharmacotherapy often worsens the symptomatology.[2] [3]The existing pharmacotherapies can have devastatingly adverse effects.[2]

[3]Among children and adolescents, the incidence [of BP] has been spiraling upward for the past half century.[2]

[3]Bipolar disorder can manifest at almost any age, but the peak period of onset is adolescence (15-19 years).[2]

Bipolar disorder can ravage the patient[1]s employment status and personal relationships, and sexuality and financial management capacities can become distorted. Lifetime risk for suicide is 19%.

During manic episodes violent behavior, such as child or spousal abuse or other antisocial behavior are common, and 10-15 % of these individuals attempt suicide.

Some typical symptoms include periods of depressed mood or loss of interest in nearly all activities; 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.[2]

[3]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.[2]

[3]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.[2]

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[3]BD is much more common in multiple sclerosis patients than in the general population.[2]

[3]Other significant comorbidities with BD are asthma and possibly migraine.[2]

Bipolar disorder is linked with schizophrenia.

[3]Family studies also suggest linkages between schizophrenia, bipolar disorder, and major depressive disorder.[2] [3]Mechanistic research suggests shared cell membrane dysfunctions.[2] [This Is The Key]

[3]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.[2]

[3]In the United States, each generation since World War II has had a higher incidence and earlier age of onset of BD.[2] [IMPORTANT] [3]On average, children with BD experience their first episode of illness 5-10 years earlier than did their parents[1] generation.[2]

[3]Children with BD often experience rapid cycling of mood states several times daily[2] which often manifests as ongoing, chronic irritability with a few hours of wellness between episodes.

[3]For many, a traumatic event triggers their first episode.[2]

[3]In the United States an estimated one million or more minors diagnosed with major depression may actually be experiencing early onset BD.[2]

A significant number of children diagnosed with ADHD actually have BD.

[3]Children and juveniles with BD are at high risk for developing addictions to drugs and alcohol.[2]

There is evidence to suggest that energy production abnormalities from mitochondrial dysfunction occurs in the BD brain. [Important for Management]

Women are also prone to develop BD after childbirth.

[3]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.[2]

[3]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[1]s own stress-coping mechanisms can inhibit neurogenesis and interfere with the establishment of circuit architecture.[2] [IMPORTANT]

[3]Social environment and major life stressors are consistently implicated in BD.[2]

[3]Latent BD can be activated by stressful life events such as death or divorce.[2]

[3]An Oextreme affective dysregulation[1] resembling bipolar disorder is increasingly being seen in children as young as 2-4 years. This can include temper tantrums, irritability, impulsiveness, aggression, hyperactivity, and poor attention.[2]

PHYSIOLOGICAL RISK FACTORS FOR BP

1) The postpartum period.

2) Low thyroid function.

3) Inadequate blood sugar supply to the brain (hypoglycemia).

4) [3]Head injury, even when associated with minimal trauma, can lead to affective psychoses and schizophrenia.[2]

[3]A high-fat and -sucrose diet (as consumed in most industrialized societies)[2] [3]leads to impairments in neuronal and behavioral plasticity without frank neurodegeneration.[2] [Important]

[3]Substance abuse is a particularly common and problematic condition for BD individuals. More than half abuse alcohol, amphetamines, cocaine, or some other substance.[2]

[3]Alcohol abuse together with BD doubles the risk of suicide.[2]

Children born to cocaine abusers are at higher risk stroke, seizures, irritability, hyperactivity/ADHD, and on to conduct disorder, mania, or

other affective illness.

Vietnam veterans who reported high Agent Orange exposure scored significantly higher on scales of depression and mania.

[3]Among psychiatric illnesses, bipolar disorder ranks second only to major unipolar depression as a cause of global disability.[2]

[3]Bipolar patients may spend as much as percent of their lives in episodes.[2]

[3]While certain behavioral interventions such as cognitive-behavior therapy and cell membrane nutrients have shown promise, the medical management of BD remains overwhelmingly pharmacological.[2]

Lithium, a naturally occurring mineral, is the single most effective and reliable drug treatment for BD. Estimates of lithium[1]s effectiveness in BD range from 36-80 %.

[3]Lithium 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.[2] It can [3]cause renal, thyroid, and cardiovascular toxicity, and lithium is a teratogen.[2] Lithium therapy frequently precipitates hypothyroidism.[2]

Many patients do not respond well to lithium, and compliance is also difficult due to the many side effects. 50 % of patients stop lithium within 10 weeks.

Valproate, an anticonvulsant, is a mood stabilizer used as an alternative or adjunct to lithium. Its adverse effects include weight gain, sedation, hair loss, and nausea. It can cause blood dyscrasias or polycystic ovary disease, liver toxicity and is a teratogen. [3]Valproate depletes the energy-yielding nutrient carnitine, so this should be supplemented to patients taking this medication.[2]

Lamotrigine is a newer anticonvulsant that significantly improves depression in BD, but it causes skin rash in approximately 15 percent of patients or more severe dermatological reactions, including the potentially fatal Stevens-Johnson syndrome.

[3]Clearly no existing medication or combination provides exceptional benefit without side effects.[2]

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[3]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). [Very Important]

Leading authorities believe (like the late David Horrobin) believe that abnormalities of the enzyme phospholipase A2 (PLA2) is the central mechanism for BP. Lithium inhibits the activity of PLA2. [3]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. 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 Oflip[1] 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.[2]

[3]Considering that the omega-3 LCFA counterbalance the omega-6 profile of the membrane, this hypothesis can be accorded further clinical relevance.[2] [Important]

The gene (or genes) controlling PLA2 is the main candidate [3]psychosis[2] gene.

[3]The omega-3 long chain fatty acids EPA and docosahexaenoic acid (DHA) have emerged as effective mood stabilizers in BD.[2]

[3]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.[2] [Stoll AL, Severus WE, Freeman MP, et al. Omega 3 fatty acids in bipolar disorder: a preliminary double-blind, placebo-controlled trial. Arch Gen Psychiatry 1999;56:407-412.] [3]This study demonstrated significantly longer remission due to EPA+DHA, and significant improvements over placebo on a variety of outcome measures.[2]

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. Several showed that [3]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.

[This is important for strict vegetarians]

[3]EPA and DHA are intrinsic to the molecular structure of the phospholipids of cell membranes, making up the Otails[1] of the molecule. The membrane[1]s phospholipids are integral to its signal transduction mechanisms. The fatty acid tails are essential to their roles in modulating the functioning of proteins in the membrane.[2]

[3]EPA and DHA lend fluidity to cell membranes[2] as a consequence of their multiple double-bonds which [3]produce a more loosely packed and Ofluid[1] membrane matrix.[2]

EPA and DHA can block calcium influx into the cell through the calcium channel, similar to calcium channel blocker medication. [IMPORTANT]

OTHER NUTRIENTS BENEFICIAL IN BIPOLAR DISORDER

Phospholipids

Phospholipids are the primary building blocks of cell membranes.

The tails of the phospholipid are esterified fatty acids, and the [3]extent of unsaturation confers degrees of fluidity on the membrane.[2]

[3]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.[2] [IMPORTANT]

[3]Lecithin (mixed phospholipid) preparations can benefit mania.[2] Lecithin, with 90% PC [PC is the major membrane phospholipid,] at a dose of 15-30 g daily, has been shown to help BD patients.

Antioxidants

[3]Bipolar disorder patients may have impaired antioxidant defenses.[2]

Manic-depressive patients have low blood glutathione and greater lipid peroxidation.

Vitamin C is a [3]pivotal nutrient for schizophrenia, and 1 g vitamin C for three weeks results in significant improvement.

B Vitamins

[3]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.[2]

[3]Folate deficiency, the most common nutrient deficiency, may be found in over one-quarter of hospitalized psychiatric patients.[2]

Folate is essential for the biosynthesis of both norepinephrine and serotonin.

Amino Acids

Several amino acids are precursors to brain neurotransmitters.

Tryptophan is metabolized to serotonin and then to melatonin.

Tyrosine is the precursor for the catecholamine transmitters dopamine, norepinephrine, and epinephrine.

Oral dosing with L-tryptophan in doses between 6 12 g daily has benefited BD patients. However, high doses of tryptophan can generate toxic metabolites.

5-Hydroxytryptophan (5-HTP) is a metabolite of tryptophan and is the immediate precursor of serotonin. Several studies indicate 5-HTP is an effective antidepressant, including in BD, with more than half the patients showing very good to moderate improvement.

The author cautions that one should not take 5-http while also taking SSRI drugs because it can cause serotonin syndrome agitation, confusion, delirium, tachycardia, diaphoresis, and blood pressure fluctuations.

Multivitamin-Minerals Other Nutrient Combinations

A broad-spectrum dietary supplement that provided B vitamins at many multiples of the RDA and a full range of essential minerals noted significant improvements on rating scales for depression, mania, and general psychiatric status. Many of the patients studied were able to get off their drugs and remained off them years later.

RATIONAL BASES FOR INTEGRATIVE BD MANAGEMENT

Lifestyle Changes are Essential

[3]Cigarette smoking is a significant contributor to depression.[2]

Nicotine stimulates the adrenal stress hormones, including cortisol.

Alcohol is a brain depressant, increases adrenal hormone output, interferes with many brain cell functions, disrupts normal sleep cycles, and contributes to hypoglycemia. [3]The resultant sugar craving initiates a vicious cycle of sugar overconsumption that ultimately exacerbates the hypoglycemia.[2]

[3]People feeling depressed or anxious tend to be especially sensitive to caffeine.[2] A person who consumes caffeine has a higher risk for depression. [3]Bipolar subjects tend to abuse caffeine as a kind of self-medication.[2] People with depression should avoid caffeine completely.

[3]Exercise may be the most powerful antidepressant available.[2] [Very Important]

Regular exercise decreases symptoms of depression, anxiety, insomnia, and malaise. [3]These benefits are perhaps related to the release of endorphins in the brain.[2]

Dietary Revision

[3]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.[2]

[3]Omega-3 fatty acids (long-chain EPA+DHA) show great promise to benefit BD.[2] In these studies, high doses were used, [3]almost 10 g EPA+DHA.[2]

[3]The Otypical[1] 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.[2]

The ratio of omega-6 to omega-3 intakes has changed from 2-4 early last century to more than 20 currently; [3]some experts believe this accounts for the decade-by-decade increased incidence of major depression.[2]

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[3]The omega-3 fatty acids are notoriously unstable without antioxidants and function best in cell membranes when antioxidant status is good.[2] [Very Important]

[3]Care must be taken to avoid fish or other foods that may carry a high load of mercury or other pollutants.[2] [Very Important]

[3]Cooking without oil or using cooking oils that resist oxidation, such as extra virgin olive oil, should be emphasized.[2]

[3]Bipolar patients should be careful of flaxseed oil, based on reports that continued intakes can trigger mania.[2]

[3]The conscientious BD patient will avoid refined foods with high burdens of sucrose, trans (hydrogenated) fats, poor nutrient content, and potentially toxic additives.[2]

Dietary Supplementation Program

Supplementation of the diet with vitamins and other nutrients is indicated.

[3]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.[2]

[3]BD patients are likely to benefit from dietary supplements that enhance intestinal detoxification and normalization, including probiotics and digestive enzymes.[2]

BD patients should have [3]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.[2]

[3]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.[2]

CONCLUSION

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Bipolar disorder is potentially devastating to the individual and society, causing social liability, lost productivity, financial costs, and a high rate of suicide.

Imaging gives clues to abnormalities in membrane phospholipid metabolites that may hold the key to understanding BD.

[3]Pharmaceuticals still have an important role to play in BD, but preferably in conjunction with comprehensive dietary supplementation.[2]

[3]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.[2]

Lithium has major adverse effects and a great many patients do not benefit from it.

Newer drugs are available, but all have frequent and troubling adverse effects.

[3]As with innumerable other diseases and disorders, conventional allopathic management of BD remains woefully inadequate.[2]

[3]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[1]s proven signal transduction actions.[2]

[3]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.[2]

[3]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.[2]

KEY POINTS FROM DR. CHRIS QUIGLEY

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1) Bipolar disorder (BD) is characterized by periods of abnormally elevated mood (mania) that cycle with abnormally lowered mood (depression).

2) Since World War II, BD has been steadily worsening with earlier age of onset, greater intensity of symptoms, and development of drug resistance.

3) BD has been spiraling upward for the past half century, especially among children and adolescents, and is very difficult to manage.

4) On average, children with BD experience their first episode of illness 5-10 years earlier than did their parents[1] generation.

5) BD is a major cause of disability and premature death from suicide.

6) The existing pharmacotherapies for BD can have devastatingly adverse effects.

7) Schizophrenia, bipolar disorder, and major depressive disorder, probably all are the result of cell membrane dysfunctions.

8) In the United States an estimated one million or more minors diagnosed with major depression may actually be experiencing early onset BD.

9) A significant number of children diagnosed with ADHD actually have BD.

10) Mitochondrial dysfunction resulting in reduced energy production occurs in the BD brain.

11) Women are prone to develop BD after childbirth.

12) Stress during pregnancy results in fetal exposure to high levels of maternal corticosteroids, resulting behavioral abnormalities and increased risk for schizophrenia and depression in later life.

13) An Oextreme affective dysregulation[1] resembling bipolar disorder is increasingly being seen in children as young as 2-4 years. This can include temper tantrums, irritability, impulsiveness, aggression, hyperactivity, and poor attention.

14) The Western high-fat and sugar diet leads to impairments in neuronal and behavioral plasticity.

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15) Lithium, is effective in 36-80 % of BD patients, but has numerous side effects, including diarrhea, polyuria, tremor, acne, taste distortion, sedation, cognitive dulling, goiter, and weight gain; renal, thyroid, and cardiovascular toxicity, and cancer.

16) Many patients do not respond well to lithium, and 50% of stop lithium within 10 weeks because of the side effects.

17) The omega-3 fatty acids DHA and EPA are effective mood stabilizers in BD.

18) The omega-3 fatty acid flaxseed oil does not benefit the BD patient, and can have adverse effects with extended use.

19) EPA and DHA have many double bonds and therefore add fluidity to cell membranes.

20) EPA and DHA can block calcium influx into the cell, which is important because calcium influx generated free radical damage and death of neurons.

21) BD patients improve with mega doses of antioxidants, B vitamins, amino acids tryptophan (5-http) and tyrosine, broad-spectrum multiple vitamins and minerals.

22) BD patients should not smoke, not drink alcohol, not eat refined carbohydrates, and not ingest caffeine.

23) The most powerful antidepressant is regular exercise.

24) BD patients should regularly exercise, consume high doses (10 g / day) EPA+DHA omega-3s

25) The typical U.S. and Western European diet is largely depleted of omega-3 fatty acids

26) Experts believe that the decade-by-decade increase of major depression is linked to the ever worsening ratio of omega-6 to omega-3 fatty acids in the diet.

27) Omega-3 fatty acids are notoriously unstable without antioxidants.

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28) Fish may carry a high load of mercury or other pollutants.

29) Cooking should be done with extra virgin olive oil.

30) [3]As with innumerable other diseases and disorders, conventional allopathic management of BD remains woefully inadequate.[2]

31) Supplementing with the omega-3 fatty acids with phospholipids and the antioxidants that protect cell membranes could replace lithium in BD management.

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