Medical Research Archives

European Society of Medicine

OPEN ACCESS

Published: June 30, 2024

Citation: Velasco-Popov V and Cooper CC, 2024. The Role of Food and Nutrition in Treating Bipolar Disorder: A Narrative Review for The Allied Health Professions, Medical Research Archives, [online] 12(6). https://doi.org/10.18103/mra.v12i6.5390

DOI
https://doi.org/10.18103/mra.v12i6.5390

ISSN: 2375-1924

REVIEW ARTICLE

The Role of Food and Nutrition in Treating Bipolar Disorder: A Narrative Review for The Allied Health Professions

Vida Velasco-Popov*, BS in Biology, UCLA; Master's in Nutrition and Dietetics Candidate, Pace University

Christen Cupples Cooper, Associate Professor of Nutrition and Dietetics, College of Health Professions, Pace University

***Corresponding author:** vv82912p@pace.edu

ABSTRACT

This narrative review analyzes the body of literature on known physiological mechanisms impacting bipolar disorder (BD) and how patient-centered nutrition in conjunction with prescribed medications may positively impact patient health outcomes. Additional topics include understanding the current state of research on nutrition and BD, impact of specific micronutrient imbalances on BD, dietary tendencies including current research on whole dietary patterns and potential applications for patients with BD. The totality of research included in this review indicate that inflammatory processes play a central role impacting health outcomes in patients with BD which can be addressed with not only medication, but also with targeted nutrition therapy.

Introduction

Bipolar Disorder (BD), also known as manic depression, affects 4.4% of Americans[1] primarily in urban areas, with the highest prevalence of disease affecting adults ages 18-29.[2] The mean onset of bipolar disease most commonly occurs during early twenties however, some research suggests a bimodal onset in some individuals between ages 15-24 and in others between 45-54 years of age.[2] In adolescent groups (ages 13-18), 2.9% have BD and 2.6% of teens struggle with severe functional (daily living activities) and cognitive impairments.[1] BD affects individuals globally with no clear differences with regards to ethnicity or sex.[2] Although studies suggest creative individuals of high socioeconomic status are at increased risk for developing BD, epidemiological studies reveal a higher prevalence of this disease in individuals of lower socioeconomic status,[2] as they may have limited access to resources such as medical care, mental health services, and food.

Furthermore, individuals with BD are at increased risk for suicide, presenting a major public health concern requiring effective care and treatment.[3] Even with consistent treatment with anticonvulsant mood stabilizers and/or antipsychotics, individuals with BD commonly experience difficulty sleeping, concentrating, energy imbalances, low self-esteem, functional impairments, and hypervigilance.[4] Treatment approaches involving psychosocial interventions have been shown to improve long-term recovery, while emerging research reveals nutrition and physical exercise can positively impact treatment outcomes.[4,5]

Manic depression includes two types, Type I (BP-I) and Type II (BP-II) which differ in severity.[4] Bipolar I affects both males and females equally involving severe manic episodes resulting in social and occupational impairment often requiring hospitalization.[4] In contrast, BP-II is more common in females and involves less severe, hypomanic episodes which do not typically lead to social or occupational impairments.[4] BD involves both manic and depressive phases which cycle over time. During manic states, individuals with BD often experience grandiose thinking, inflated self-esteem, excessive talkativeness, reduced need for sleep, and participation in risky behaviors.[6] In contrast, during depressive states individuals with this disorder may present with poor memory, difficulties with concentration, feelings of isolation, and potential suicidal ideation.[6] Without adequate treatment, these phases can cause severe social and/or physical impairments making it difficult to function in society.

With regards to neurotransmitter changes in the brain, research suggests noradrenaline (or norepinephrine) levels are generally low in individuals with BD but increase during manic phases.[7] Norepinephrine is responsible for the body's fight-or-flight response, activating in response to perceived danger. Additionally, research reveals dopamine and GABA levels increase during manic states but decrease during depressive states.[7] Dopamine plays a major role regulating mood and motivation, serving as the most influential neurotransmitter contributing to changes between manic and depressive phases.[7] GABA acts as an inhibitory neurotransmitter and is involved in mood stabilization. With regards to serotonin, research suggests this neurotransmitter plays a large role in BD; however, its mode of influence is largely unknown.[7] Current research looking into the potential applications of key micronutrients and dietary patterns unveil potential connections between nutrition and these relevant neurotransmitters as discussed in more detail in the preceding pages.

To date, the biological basis of BD remains unknown though genetic and environmental factors are thought to influence disease development.[2] Research suggests children have a tenfold risk of developing the disease if their parents have BD, though the disease does not follow typical Mendelian Inheritance patterns.[8,2] Though the precise mechanism of inheritance is still widely unknown, with genome-wide association studies, researchers have identified several susceptible loci responsible for the onset of BD.[8] Currently, 19 significant loci (specific locations within the chromosome where genes exist) have been identified as contributing to the onset of disease, however, single bipolar specific loci have not been identified.[8] Additional studies looking at epigenetic effects, suggest certain environmental factors such as stressful life events, substance abuse, and inflammation all contribute to the expression of genes associated with BD.[9,2] From a nutritional perspective, these findings are particularly significant in that there are many foods and spices that can play a supportive role in helping reduce body inflammation.

Though bipolar disease can be quite devastating on its own, there are several associated comorbidities contributing to increased health care costs and mortality rates in this population. Individuals with bipolar disease are at higher risk for obesity, metabolic syndrome, Type 2 diabetes, and cardiovascular disease, reducing life expectancy by 20-30% compared to the general

population.[2,10] In addition, new research reveals increased rates of irritable bowel syndrome (IBS) in patients with BD causing intestinal malabsorption of key nutrients and increased gastric distress.[2] Although there are many comorbidities associated with BD, these conditions are largely modifiable with targeted lifestyle interventions such as balanced nutrition and regular physical exercise.

Although not well-known as evidenced by the dearth of research on this topic, it is possible that symptoms of BD may be attenuated with medical nutrition therapy, including changes in overall diet and/or with vitamins and minerals that may help to attenuate the symptoms of BD. The purpose of this narrative review is to inform not only registered dietitian nutritionists, but an interprofessional audience, about the potential dietary factors affecting individuals with BD. Dietitians, physicians, psychiatrists and other healthcare professionals who work with BD individuals may learn about relevant evidence-based dietary factors, perhaps in conjunction with medication to positively support symptoms and long-term health outcomes.

Methods

This study is a literature review of studies conducted on the potential effects, therapeutic uses and linkages between food, nutrition and bipolar disorder. Between September 2023 and February 2024, PubMed was searched for relevant, peer-reviewed studies on BD and nutrition. The search utilized the keywords: "bipolar disorder and:" manic depression, manic depressive disorder, bipolar I, bipolar II, nutrition, nutrients, micronutrients, minerals, vitamins, nutrient imbalances, mechanisms, dietary patterns, diet, micronutrient deficiencies, micronutrient insufficiencies, prescribed diet, therapeutic diet, lifestyle interventions, dietary interventions. Journals from across the health professions were included in the study. Excluded studies were: those published more than five years before publication of this review and articles that addressed other mental health conditions such as major depressive syndrome, hypothymia schizophrenia. Studies that covered nutrition and two or more mental health disorders were included as long as the study included BD. The review did not limit the span of studies to only those published in the United States.

Results

DIET PATTERNS AND BIPOLAR DISORDER

Common dietary patterns in individuals with bipolar disease primarily include foods high in calories, saturated fat, and sugar or energy-dense, nutrient-poor foods.[10,11,12] In a recent study comparing intake habits in bipolar individuals to healthy controls, using food frequency questionnaires, researchers found eating tendencies fell into four main categories 1. Western, 2. Pro-healthy Carbohydrates, 3. Unhealthy Snacks, and 4. Meats and Potatoes.[13] When compared to healthy controls, researchers found individuals with BD had significantly lower Mediterranean Diet scores and higher baseline triglyceride and blood glucose levels.[13] Numerous studies have shown individuals who eat a diet rich in fruits, vegetables, whole grains, legumes, nuts, seeds, with moderate quantities of fish and limited amounts of sweets, red meat and processed foods reduce risk for metabolic disorders, and cardiovascular disease promoting longevity.[13,14] Furthermore, there is some evidence suggesting anti-inflammatory properties of the Mediterranean Diet may provide neuroprotective health benefits further supporting bipolar disease outcomes.[14]

MEDITERRANEAN DIET

A Mediterranean dietary pattern is primarily characterized as a plant-based diet rich in fruits, vegetables, whole grains, legumes, plant oils, nuts, and seeds with moderate amounts of seafood, dairy, eggs, and poultry.[14] Substantial research, including longitudinal studies such as the Nurses' Health Study, support its use in reducing risk for diseases such as cardiovascular disease, type 2 diabetes, and Alzheimer's disease. However, there is little existing research on its applications for patients with BD. In one observational study involving 113 euthymic bipolar disease patients and 160 healthy controls found individuals with BD with significantly lower Mediterranean Diet scores compared to individuals without this disorder.[13] In addition, it was found that individuals with BD had BMI scores above 25, higher levels of fasting triglycerides and glucose levels, and significantly larger waist circumferences compared to participants in the control group.[13] These physical characteristics all increase overall risk for developing cardiovascular disease, and diabetes which are common comorbidities found in individuals with BD.[2,10] As mentioned previously, current research suggests individuals with BD experience mitochondrial and glucose metabolism dysfunctions which further contribute to developing these chronic diseases. Looking at the dietary profiles of individuals with BD, we find higher consumption of processed foods, and sweets. Such dietary tendencies may relate to possible heightened taste for simple carbohydrates due to mitochondrial dysfunctions which could contribute to lower Mediterranean Diet scores, though no current research exists on this topic.

Due to its emphasis on a variety of fruits and vegetables, the Mediterranean Diet seems to confer anti-inflammatory properties which may offer neuroprotective benefits for individuals with bipolar disease. Studies have identified lower levels of antioxidants such as vitamins C, E, A, and D in individuals with bipolar disease as well as lower levels of zinc (during depressive phases), manganese, iron, and nickel.[14] Foods such as dark green leafy vegetables, nuts, seeds, berries, and fruit that are cornerstones of the Mediterranean Diet may help address commonly observed micronutrient deficiencies. Considering there are very few studies looking at overall dietary patterns for patients with bipolar disease, further research is needed to explore specific effects of the diet over time. With its promotion of plant foods containing valuable antioxidant vitamins and minerals and its emphasis on healthful fats, this diet may support improvements in the health of individuals with BD.

SUGARS

As mentioned previously, high sugar consumption is common in individuals with BD.[7,11,12] Though physiological mechanisms underlying this trend are still not fully understood, a recent research article investigating the relationship between high fructose corn syrup and uric acid production in bipolar individuals provides us with some additional insight into this topic. From an evolutionary perspective, during periods of starvation, metabolic survival mechanisms activate to maintain energy balance. This process involves the metabolism of fructose in the absence of carbohydrates to provide energy, stimulating the body to store fat in the liver, blood, and adipose tissue.[11] Although bipolar individuals may not regularly undergo periods of true starvation due to lack of food per say, it is possible that an unbalanced diet, heavy in high fructose corn syrup (present in most packaged sweets and sugar sweetened beverages) could falsely activate these starvation mechanisms. This, in addition to increased fat storage in adipose cells, is known to decrease cell insulin sensitivity. Furthermore, high sugar consumption in individuals with BD is related to hypercortisolemia, since cortisol counteracts the activity of insulin, releasing stored glucose into the bloodstream.[12] As individuals with bipolar disease are at greater risk for developing type 2 diabetes, high intake of sugary foods is especially concerning.[11]

Additionally, fructose metabolism results in the production of uric acid, a waste product which in excessive amounts can lead to mitochondrial oxidative stress and decreased oxidative phosphorylation.[11] Research points to excessive uric acid production as contributing to insulin resistance, fat synthesis, and increased blood pressure.[11] All key features involved in metabolic syndrome. A recent meta-analysis of 44 studies, 1,979 bipolar individuals and 1,788 healthy controls revealed increased uric acid levels during periods of mania and euthymia (time between manic and depressive episodes) compared to healthy controls.[15] These findings suggest elevated uric acid levels, common in individuals with BD, may also influence manic states. In another article, researchers linked over-activation of survival pathways with increased impulsive tendencies and manic symptoms in bipolar individuals though further studies are needed to fully explore this relationship.[11] As high uric acid levels pose a major concern for patients with BD, more dietary research is needed on exploring potential applications of N-acetylcysteine for potentially helping lower uric acid levels. Considering both immediate and long-term negative effects of high sugar consumption, limiting consumption of refined sugar and high fructose corn syrup may offer protective health benefits for bipolar individuals.

ANTIOXIDANTS

Current research looking into the connection between oxidative stress and its effects on both mitochondrial, and dopamine dysfunction help us in our understanding of BD. In a postmortem study examining blood and brain samples in young bipolar individuals, researchers found evidence revealing increased oxidative stress with corresponding oxidative damage.[15] These results further underlie the importance of managing oxidative stress, especially for individuals with BD. To date, the known etiology of BD involves several key factors including oxidative stress, increased inflammation, mitochondrial disturbances, and neurotransmitter imbalances.[15,16]

In a recent review, researchers found increased dopamine levels present during manic states contribute to the production of reactive oxidative species which damage lipids, protein, DNA and RNA.[15] The production of free radicals occurs primarily through two main processes, spontaneous auto-oxidation of dopamine or via enzymatic catalysis; both of which play a role in contributing to manic symptoms. [15] Additionally, BD is associated with increased calcium signaling, likely related to oxidative stress due to the presence of free radicals.[8,15] Recent studies indicate how overproduction of reactive oxidative species or free radicals in the mitochondria can damage calcium regulating proteins such as calcium-ATP synthase.[15] Damage to these regulatory proteins disrupt mechanisms maintaining calcium homeostasis leading to increased blood calcium levels, as

commonly observed in individuals with BD.[15] Research suggests poor regulation of calcium contributes to bipolar disease symptoms as noted in a recent review though no current studies address potential effects of limiting dietary consumption of calcium.[15] Further studies are needed to fully understand whether limiting consumption of calcium may play a role in helping mitigate symptoms of BD.

Individuals with BD are found to have reduced levels of neuroprotective vitamins such as folate, and vitamin B12 as well as lower levels of antioxidant micronutrients including vitamins C, E, A, D, and DHA (a component of omega-3 fatty acids) compared to individuals without bipolar disease.[10,14] Antioxidants are essential for reducing oxidative stress, which may lead to cellular damage, mitochondrial dysfunction, alterations to genetic material, and increased levels of inflammation.[15] Considering the role of inflammation in the pathology of BD, antioxidants and other potentially beneficial nutrients such as CoQ10, N-acetylcysteine, and tryptophan present opportunities for research. Research on low level antioxidant micronutrients in BD individuals has primarily been studied in the context of overall dietary patterns such as the Mediterranean Diet rather than individual antioxidant effects. From a nutritional perspective, the inclusion of antioxidants in the context of whole foods is generally preferred over supplementation as nutrients from food are more readily absorbed in their natural form. Presently, vitamin D remains the only isolated vitamin with extensive research looking into its application for patients with BD.

In a recent review, individuals with BD were found to have significantly reduced levels of vitamin D compared to the general population.[17] Vitamin D plays a variety of different functions within the body including bone mineralization, intestinal absorption of calcium, neuroregulation, and cell differentiation, all of which are critically important for supporting general health. Additionally, in a cross-sectional study with 118 individuals with BD, researchers found individuals with the disorder were 4.7 times more likely than the general population to present with a vitamin D deficiency.[18] These findings further underlie the relevance and interest in studying the effects of vitamin D for individuals with BD. Though vitamin D plays a role in neuroregulation via binding to receptors within the central nervous system, supplementation of vitamin D in individuals with BD does not appear to improve symptoms of this disease.[17] Given current findings, it appears there are no studies to date that suggest significant correlations between vitamin D supplementation and the reduction of bipolar symptoms.[17] Though vitamin D may not directly improve symptoms of BD, it remains important to consume adequate dietary sources of vitamin D to address potential deficiencies.

With regards to mineral imbalances, a recent systematic review revealed individuals with BD commonly have decreased serum zinc, manganese, iron, selenium, and sodium and increased copper and calcium levels compared to the general population.[14,15] A review of the literature suggested that zinc, the only mineral studied for its benefits for BD.[14, 34, 35]

CoQ10

CoQ10 is an important electron acceptor in the mitochondrial transport chain. This enzyme plays a major role in helping produce ATP (our body's main currency for energy) during aerobic cellular respiration while neutralizing free radicals. There are no current dietary reference intake guidelines for CoQ10, though this nutrient can be found in meat, fish, poultry, as well as certain plant oils such as olive, corn, and canola.[19] In a recent study comparing the effects of CoQ10 supplementation in bipolar patients vs. placebo groups, researchers observed reduced oxidative stress and inflammation with CoQ10 supplementation suggesting a potentially beneficial role for this nutrient for individuals with BD.[20] The trial was conducted over 8 weeks with 69 bipolar patients all experiencing depressive phases. Participants were randomly assigned and instructed to continue normal treatment regimens throughout the trial. The treatment group consisted of 36 individuals receiving 200 mg of CoQ10 per day while the placebo group included 33 individuals receiving a placebo pill the same size, shape, and color.[20] Blood samples were taken and analyzed for inflammatory markers both at baseline and at the end of the trial. Additionally, depression scores were recorded at baseline and at the end of the trial using MADRS (a clinical interviewing scoring system to assess depression severity).[20] Researchers found an overall reduction in inflammatory markers including TNF-a, IL10, and NO in the CoQ10 group compared to the placebo group.[20] This research provides strong evidence for the application of CoQ10 in helping mitigate systemic inflammation, especially pertinent for individuals with BD. In addition, researchers observed increased total antioxidant capacity (TAC) and total thiol group (TTG) levels in the trial group, indicating greater capacity for managing free radicals.[20] Depression scores improved significantly among the CoQ10 group, further demonstrating beneficial effects for bipolar individuals.[20] Although this study suggests

that there is evidence supporting CoQ10 use in bipolar individuals, study limitations included limited sample size and omission of whole food sources containing CoQ10. Future studies aimed at addressing these limitations may prove beneficial, as many individuals with BD may not have the ability or resources to invest in high-cost supplements.

With further studies and meta-analyses, research may support CoQ10 supplementation as a routine part of nutrition therapy in helping manage oxidative stress in patients with BD. Development of specific guidelines for CoQ10 supplementation regarding dosage, frequency, and long-term effects are still underway though intake of whole foods rich in CoQ10 may still benefit individuals with BD experiencing depressive states. Further studies focusing on dietary intake of CoQ10 are needed to further outline best therapeutic practices for disease management in this population. Nonetheless, a recent systematic review published in 2022 confirms the strong, but limited number of studies supporting CoQ10 supplementation in bipolar individuals.[14]

N-ACETYLCYSTEINE

N-acetylcysteine (NAC) is an antioxidant derived from the amino acid L-cysteine found in high concentrations in foods such as soybeans, quinoa, and whole wheat flour with promising antidepressant health implications for patients with BD.[21,22] Ingestion of NAC leads to increased production of glutathione, a major antioxidant important for reducing oxidative stress.[23] Recent studies exploring the mechanism of action of NAC reveal this substance may increase extracellular glutamate while inhibiting glutamate neurotransmission, thus producing antidepressant effects.[22] Patients with reduced NAC were found to have increased glutamine uptake due to poor glucose metabolism.[24] Furthermore, NAC may provide anti-inflammatory and protective mitochondrial properties, as well as serotonin modulating activity particularly applicable for bipolar patients experiencing depressive phases.

In a recent 12-week, double blind randomized control trial, researchers looked at the effects of NAC supplementation on symptoms of depression. Sixty-seven participants with BD and major depressive disorder were randomly assigned to control groups (placebo capsules) or NAC groups (1.8g of NAC/day).[25] Clinical and demographic information was gathered as well as clinical depression scores using the Hamilton Depression Rating Scale (HDRS), Hamilton Anxiety Rating Scale (HAM-A), and Clinical Global Impression (CGI) score, measuring symptom severity and overall response to treatment.[25] Additionally, blood samples were taken both at baseline and at week 12 to further determine any significant differences between groups as well as effects on inflammation via CRP levels.[25] Individuals in the NAC group with high CRP levels at baseline (>3mg/L) had significant reductions in depression symptoms in all scoring categories.[25] These findings suggest there is potential application of NAC in helping reduce symptoms of depression. Additionally, the NAC group had significantly reduced CRP levels at the end of the trial when compared to the placebo group. The NAC group had significant reductions of uric acid levels as compared to controls and individuals with lower baseline CRP levels (<3mg/L).[25] Researchers also found participants in the NAC group performed better at work (higher productivity, reduced work impairment, and fewer work absences) as compared to the placebo group suggesting inclusion of this nutrient may also positively contribute to work performance.[25]

Another study exploring the potential effects of NAC supplementation on symptoms of mania and hypomania in pediatric individuals with BD revealed significant improvements in both manic and depressive symptoms.[23] It also provided preliminary evidence supporting the safety and tolerance of NAC use for children with BD.[23] The results supported previous findings. A systematic review analyzing the potential role of NAC in patients with bipolar disease concluded that multiple studies found significant improvements in depressive symptoms.[14] In addition, a recent review on the effects of various therapeutic agents on patients with BD suggested there is evidence supporting complementary use of NAC with medications to reduce BD-related symptoms of depression.[15] Current findings provide promising applications for NAC for improving symptoms of depression, reducing systemic inflammation, and improving workplace performance all of which could have life changing implications for individuals with BD. As the application of NAC for managing symptoms of mania was only studied in pediatric populations, future studies aimed at examining manic symptoms in adults seems of particular relevance for future research.

TRYPTOPHAN

Tryptophan is an essential amino acid which cannot be synthesized by the body and must be obtained through the diet. This essential amino acid can be found in foods such as lean meats, salmon, tofu, beans, eggs, pumpkin seeds, oatmeal, and milk, among other sources.[36] Tryptophan plays important roles including protein synthesis, energy

metabolism, nerve function, and modulating immune reactions.[27] Additionally, this nutrient is particularly relevant for individuals with BD as it can be broken down and converted into serotonin, a key neurotransmitter involved in the pathology of BD.[27] Tryptophan is also needed for the production of niacin (vitamin B3), important for brain function and melatonin, a key hormone involved in maintaining circadian rhythms regulating sleep cycles.[27]

A recent meta-analysis of 21 studies involving individuals with BD explored the downregulation of catabolic pathways involving tryptophan in patients with BD, suggesting that tryptophan from the diet may support these important pathways.[27] Another recent review cited evidence for both inflammation and tryptophan metabolism as major processes involved in the physiological mechanism of BD.[28] Preliminary research suggests that including sufficient tryptophan in the diet for patients may provide therapeutic benefits needed for supporting tryptophan catabolizing pathways.

A postmortem study of bipolar brains found decreased levels of serotonin metabolites with the presence of inflammation.[28] These findings are consistent with signs of upregulation of tryptophan in the kynurenine pathway as opposed to its use in the serotonin pathway due to increased levels of inflammation. Tryptophan is needed to produce niacin, a key vitamin important for energy production among other functions. Additional research suggests a deficiency of niacin negatively affects preserving the gut barrier, and mitigating inflammation which in turn may lead to overactivation of tryptophan in the kynurenine pathway.[30] Overactivation of the kynurenine pathway can result in neurotoxicity which may affect symptoms of BD though further studies are needed to explore this potential connection.[28] Current evidence has not yet established a clear connection between tryptophan and the symptomology of BD. Considering the different metabolic pathways involved in patients with BD, it seems further studies are needed looking at probiotics, systemic inflammation, neurotoxicity, and tryptophan levels to fully understand potential applications.

PROBIOTICS

Probiotics are beneficial microbial species thriving primarily within the gut carrying out a variety of different functions. These functions include, but are not limited to, reducing inflammation, preserving gut integrity, and supporting the body's immune response. Naturally occurring probiotics can be easily obtained through the consumption of fermented foods which include kefir, tempeh, cheeses, and sauerkraut to name a few. Recent research into the gut-brain axis suggests a potential role for probiotics as a co-treatment option to potentially improve symptoms of BD.

In a longitudinal study involving 115 individuals with BD and 64 healthy controls, researchers performed a stool microbiota analysis, finding decreased populations of Firmicutes and Faecalibacterium species which correlated with depressive symptom severity.[31] These findings provide us with greater insight into how gut dysbiosis can negatively impact patients with BD especially during depressive phases. Additionally, in a randomized control trial with 66 bipolar patients admitted with mania, researchers discovered a negative correlation between microbial populations of Lactobacillus and Bifidobacterium (probiotic bacteria), and rehospitalizations post-discharge.[32] Patients in the experimental group were given a daily probiotic supplement containing Lactobacillus GG and Bifidobacterium Lactis Bb12 strains of bacteria over 24 weeks while individuals in the control group were given a placebo pill.[32] Interestingly, patients in the probiotic group had fewer hospital readmissions and shorter admission stays - 182 fewer days compared to those in the control group.[32] Furthermore, these effects were amplified in individuals with increased systemic inflammation above the 50th percentile, suggesting an approximate 90% reduction in hospital readmissions.[32]

As there is much evidence supporting the role of inflammation in the pathophysiology of BD, it is important to consider the potential application of probiotics for patients with BD. Though further studies are needed to fully understand how probiotics may support patients with BD, probiotics do not pose any harm for non-immunocompromised patients or for those who have not undergone recent surgery.[33] Additionally, the Academy of Nutrition and Dietetics notes Lactobacillus, Bifidobacterium, Streptococcus Thermophilus, and Saccharomyces genera all have extensive public safety records supporting their use in outpatient settings.[33] As a matter of dietetics practice, probiotics within foods are preferred over probiotic supplements.

ZINC AND OTHER MINERALS

Zinc is an important mineral carrying out several different functions including supporting DNA binding and gene expression, aiding insulin release, wound healing, neurotransmission, and supporting the immune system. With regards to neurotransmission, zinc plays a role in excitatory signaling involving glutamate, norepinephrine, and epinephrine.[34] Though there is extensive research

looking at the role of zinc and individuals with depression, very little research exists in the context of patients with BD. In a recent study looking at serum zinc concentrations in individuals with bipolar I and II, researchers found decreased levels of zinc in bipolar I individuals compared to healthy controls during depressive phases.[34] These findings suggest a potentially broader role for zinc extending beyond its known applications for individuals with major depression. In addition, researchers found increased zinc levels in bipolar individuals experiencing mania also correlated with frequency of manic episodes experienced over one year.[34] Research suggests that zinc levels fluctuate over the course of the disease decreasing during depressive states and increasing during manic states. Due to the cyclic nature of BD with periodic fluctuations over time, further studies are needed to determine if zinc supplementation may be indicated and how timing might influence effectiveness.

In another study looking at zinc serum concentrations in stabilized bipolar individuals, researchers found zinc levels were elevated in stabilized individuals though levels were unrelated to inflammatory markers and did not correlate with disease severity.[35] Though zinc is an essential micronutrient for health in general, due to the nature of BD and lack of understanding with regards to mechanism of action, continuous supplementation is not advised. Rather, zinc levels may serve as a biomarker helping distinguish between different phases of BD as levels are generally low during depressive states and elevated during manic states. Potential future studies might look at the impact of short-term consumption of zinc rich foods during depressive states, however general recommendations concerning zinc cannot be made at this time.

Considering other minerals relevant to BD, a recent genome-wide association study suggests that there is a correlation between serum magnesium and copper levels and BD genetic activation. Analyzing genetic data from 20,129 patients with BD and 21,542 healthy controls, researchers found magnesium and copper may contribute to epigenetic activation or deactivation of SELENBP1, a genetic biomarker for BD.[36] Researchers found increased serum magnesium levels were positively correlated with BD, while the opposite was true for serum copper levels.[36] These findings suggest magnesium may play a role in the activation of SELENBP1 gene while copper may play an inhibitory role. These preliminary studies suggest copper may play a beneficial role for patients with BD, however there are no current studies on the role of copper in patients with BD. Further studies are needed to fully understand the mechanism of action involving epigenetic changes related to these key minerals as well as additional genes involved in bipolar disease.

OMEGA-3 FATTY ACIDS

Omega-3 fatty acids carry out a variety of different functions as they possess anti-inflammatory properties, play a supportive role in neurodevelopment, maintain cell membrane fluidity, provide constructive support for the phospholipid bilayer (cell membrane border), and aid in modulating synaptic neurotransmission.[37,38] Key sources of omega-3 fatty acids include fatty fish, walnuts, flaxseeds, chia seeds, and marine microalgae.[39] Though applications of omega-3 fatty acids for supporting general brain health are well known, recent studies suggest additional applications for individuals with BD. In a recent epidemiological study, researchers found lower prevalence of BD globally in areas with high seafood consumption compared to areas with low seafood consumption.[13] As seafood is rich in anti-inflammatory omega-3 fatty acids, these findings provide us with some insight into the potential neuroprotective effects of omega-3 fatty acids for individuals with BD.

A systematic review found decreased levels of EPA and DHA (components of omega-3 fatty acids) and higher ratios of omega-6 to omega-3 fatty acids in bipolar individuals compared to healthy controls.[14] As omega-6 fatty acids are proinflammatory compared to omega-3 fatty acids, a higher ratio of omega-6: omega-3 fatty acids reveal signs of systemic inflammation. These findings are of particular importance for patients with BD as we know inflammation plays a major role in the etiology of this disease. Though there are a limited number of studies looking at the anti-inflammatory effects of omega-3 fatty acids on patients with BD, there are studies looking at the effects of omega-3 fatty acids on mood variability and cognitive function.

In a 12-week intensive double-blinded randomized control trial, 82 participants with BD receiving pharmaceutical treatment were randomly assigned to a high omega-3 diet (1500mg/day), a low omega-6 fatty acid diet (2% of calories) or to a standard American diet (150mg omega-3 and 7% calories from omega-6).[38] Participants were required to meet with a dietitian six times throughout the study to review diet adherence, pick up food supplies, go over dietary recall information, and for dietary counseling.[38] In tracking mood variability, participants were asked to report changes in mood, energy, speed of thoughts, impulsivity thoughts and actions, anxiety,

irritability, and pain using an ecological momentary analysis (EMA) sampling model twice a day over the course of the study.[38] At the end of the study, researchers found significantly reduced variability in mood, irritability, energy, and pain with the omega-3 fatty acid rich diet.[38] These findings provide preliminary evidence to support the application of an omega-3 rich diet for helping stabilize mood changes in individuals with BD.

In another study looking at the cognitive effects of omega-3 supplementation (1250mg) on bipolar participants in euthymic states (not in manic or depressive states), researchers did not find any significant improvements in cognition.[37] Only healthy controls experienced improvements in cognitive function over the course of the trial.[37] Though bipolar individuals did not show signs of cognitive improvement, it is important to note that these participants had significantly lower GAF scores (Global Assessment of Functioning) at baseline, more hospitalizations, and lower initial levels of plasma DHA compared to healthy controls.[37] It is possible that individuals with BD may have differences in metabolism of omega-3 fatty acids requiring higher dosages compared to healthy individuals to achieve similar cognitive improvements. Additional research looking into optimal doses of omega-3 fatty acids as well as optimal DHA to EPA ratios of omega-3 fatty acids are needed to fully understand all potential applications for individuals with BD.

Though current research does not support the use of omega-3 fatty acids for improving cognition in patients with BD, several studies have shown regular consumption of seafood rich in omega-3 fatty acids is associated with reduced prevalence of BD.[13,14,38] These findings imply regular consumption of omega-3 fatty acids may provide a neuroprotective function potentially, helping reduce risk for developing BD. While current research looking into the effects of omega-3 fatty acids seem promising, additional studies are needed to develop concrete nutrition guidelines to best support patients with BD.

VITAMIN B6, B9, AND B12

Vitamin B6 (pyridoxine), B9 (folate) and B12 (cobalamin) serve many important functions throughout the body, donating methyl groups for protein, lipids, nucleic acids, neurotransmitters, and hormones.[40] These vitamins can be found in foods such as dark green leafy vegetables, beans, sunflower seeds, salmon, chickpeas, eggs, and fortified nutritional yeast just to name a few sources.[41] As noted previously, individuals with BD have lower levels of folate and vitamin B12 compared to individuals without this disorder.[10] These key nutrients are also involved in the methionine synthase complex, converting homocysteine to methionine to SAM, an important cofactor for many different methyltransferase enzymes functioning in a variety of different metabolic pathways throughout the body.[40] Additionally, vitamin B6 is needed to allow for the conversion of homocysteine into glutathione, our body's natural antioxidant system critical for reducing oxidative stress.[40] Inadequate quantities of these key nutrients, this can lead to excessive homocysteine, increasing risk for cardiovascular disease, amyloid buildup, cognitive problems, mitochondrial dysfunction, and damage to DNA.[40] Recent studies suggest low folate, vitamin B6 and vitamin B12 levels may play a role in psychological disorders including BD, however current research does not support their use for improving symptoms of this disorder.[30,40]

Results from a recent study suggested that 40-65% of B vitamins are produced by human intestinal microbiota.[30] These findings highlight the importance of supporting a healthy gut microbiome, especially for individuals susceptible to B vitamin deficiencies. As inflammation plays a major role contributing to the pathology of BD, comorbidities such as IBS with associated gut dysbiosis, may partially explain why individuals with BD are at increased risk for B vitamin deficiencies.[2] Key probiotic bacteria of the gut such as Streptococcus thermophilus, and Lactobacillus acidophilus have been shown to increase the production of folate concentration by more than 200%, revealing the importance of probiotics for helping address vitamin B deficiencies.[30] Furthermore, 86% of daily reference intake for vitamin B6, and 31% of vitamin B12 can be produced by human gut biota (excluding Fusobacteria) demonstrating the role of probiotics for ensuring adequate levels.[30] Lastly, it seems pertinent to note that valproic acid, a medication used to treat BD, can lead to folate and vitamin B12 deficiencies.[30] Similarly, BD patients taking metformin (for insulin resistance) are also at increased risk for vitamin B12 deficiencies due to known drug-nutrient interactions associated with this medication.

Although there is scant research on bipolar symptoms and vitamin B supplementation, individuals with this disorder are at increased risk for deficiencies due to tendencies toward following Western dietary patterns.[13] Western dietary patterns commonly observed in this population are low in vitamin B6, folic acid, and vitamin B12, further increasing risk for developing micronutrient deficiencies.[13,40] Consuming a well-balanced diet

rich in B vitamins may help BD individuals to maintain overall health and manage symptoms.

Special Diets

KETOGENIC DIET

Though the ketogenic is primarily used in the context of patients with epilepsy, there is preliminary research on potential applications for patients with BD. A ketogenic diet is low in carbohydrates, high in fat, and contains moderate quantities of protein. Thus, this dietary pattern results in the use of ketone bodies over glucose to produce energy.[42] When the body enters the state of ketosis, there is an increase in glutathione synthesis (the body's natural antioxidant system) reducing oxidative stress.[42, 24]

Current research suggests individuals with BD experience mitochondrial dysfunction due to impaired glucose metabolism as evidenced by increased levels of intermediates such as pyruvate, isocitrate, and alpha-ketoglutarate (involved in the breakdown of carbohydrates).[24] Overproduction of these intermediates lead to disruptions in oxidative phosphorylation or ATP production resulting in a shift toward glycolytic ATP production with lactate as a byproduct.[24] Individuals with BD generally have increased levels of lactate compared to healthy individuals.[43] When lactate is actively oxidized, reactive oxidative species in the mitochondria are produced, resulting in increased oxidative damage.[44] Research suggests that a ketogenic diet may decrease oxidative stress in the mitochondria, hence its potential application for patients with BD.[24]

In a recent literature review and case study of a 31-year-old male with BD, researchers followed the progress of this individual over a period of three years while following a ketogenic diet. During the first year of the trial, the individual primarily followed a Mediterranean Diet high in fat reporting improved mood and sleep with no significant changes in BMI.[42] In year two of the trial, the patient followed a strict ketogenic diet consisting of "15% protein, 80% fat, and 5% carbohydrates" with most fat from omega-3 and omega-6 fatty acids as well as medium chain triglycerides.[42] Again, the patient noted similar improvements as before, but this time experienced longer periods of remission lasting 2-4 weeks.[42] During the third year of the trial, the patient added one day of fasting every 7-10 days to increase states of ketosis.[42] The patient reported no symptoms of depression, and complete remission allowing the patient to discontinue quetiapine treatment and remain only on a very low dosage of lamotrigine (100 mg per day) without experiencing any symptoms of depression or hypomania.[42] These preliminary findings suggest diet could play a major role in helping improve disease outcomes for patients with BD.

Researchers studied how ketosis may lead to decreased concentrations of glutamate allowing the conversion of glutamine to GABA.[42] GABA is primarily an inhibitory neurotransmitter which is typically reduced in patients with BD.[7] Considering mitochondrial and glucose metabolism dysfunctions present in BD patients, the ketogenic diet may offer a promising application, with its potential to reduce the presence of free radicals.[42] Reduction in free radicals decreases inflammation which may provide therapeutic benefits for BD patients. There is preliminary evidence to suggest that the replacement of polyunsaturated fat with saturated fat sources may not increase risk for ischemic heart disease.[42] Additional studies are needed to explore this topic.

In a recent systematic review, researchers analyzed 48 articles with trial periods ranging from 2 weeks to 3 years and found mixed quality evidence supporting the application of a ketogenic diet in individuals with bipolar disease.[45] At this time, additional longitudinal randomized controlled trials are needed to fully assess current evidence and ensure patient safety prior to recommending a ketogenic diet for individuals with BD.

In a retrospective study exploring the effects of a ketogenic diet on 31 inpatients with psychiatric disorders (12 patients with BD), researchers found statistically significant improvements in depression, and severity of illness scores (CGI-S) following the trial.[46] For this study, a ketogenic diet was defined as containing no more than 20g of carbohydrates (5%), 15-20% of calories from protein, and 75-85% of total calories from fat daily.[46] Of the patients with BD, most participants were also taking diabetes medications. The study resulted in 7 out of 12 participants with BD reducing their medication dosages.[46] These results are consistent with other studies which have linked the ketogenic diet with improvements in insulin sensitivity.[46] Though research on the impact of insulin resistance on oxidative phosphorylation in patients with BD is ongoing, some studies suggest that increased rates of insulin resistance lead to dysfunctions in glucose metabolism.[24]

Reference	Outcomes	Description	Findings	Number of Participants (studies)	Certainty of Evidence (High/Moderate/Low/Very Low)	Comments
Saunders EFH et al. (2021)	Mood Stability	The study investigated the preliminary efficacy of a high n-3 plus low n-6 (H3-L6) dietary intervention in improving mood stability in Bipolar Disorder (BD) compared to a control diet with usual U.S. levels of n-6 and n-3 polyunsaturated fatty acid (PUFA) intakes	Variability in mood, energy, irritability, and pain as measured using EMA was reduced in the H3-L6 group compared to the CD group. No significant differences in mean ratings of mood symptoms, or any other symptom measures, were detected.	82 participants randomized; 70 completed at least 2 EMA surveys	Moderate	Preliminary efficacy shown; further research needed
Rowland T; Marwaha S (2018)	Epidemiology and risk factors for bipolar disorder	This article reviews the epidemiology of bipolar disorder, along with demographic, genetic, and environmental risk factors	While numerous genetic and environmental risk factors have been identified (childhood trauma, pre and perinatal factors, stressful life events, substance abuse, medical comorbidities, etc.), the attributable risk of individual factors is often small. Medical comorbidities of BD such as IBS and asthma, which may point towards shared inflammatory pathophysiology.	N/A (multiple studies included in the review)	Low	Some factors have strong evidence supporting their association with bipolar disorder, but none have sufficient evidence to establish causality
Jones GH, Vecera CM, Pinjari OF, Machado-Vieira R. (2021)	Inflammatory markers in Bipolar Disorder	The review summarizes the current understanding of inflammatory signaling mechanisms in bipolar disorder (BD), including the role of cytokines, chemokines, and immune cells in the pathophysiology of BD.	Increased levels of pro-inflammatory cytokines, such as IL-1β, IL-6, TNF-α, and IFN-γ, have been consistently found in patients with BD compared to healthy controls. Additionally, peripheral immune cell dysfunction has been observed in BD.	N/A (multiple studies included in the review)	High	Covers current understanding of key metabolic pathways involved in BD including the kynurenic pathway
Luciano M, Sampogna G, Amore M, et al. (2022)	Physical Activity and Diet Improvement	The study investigated the effectiveness of a 6-month real-world randomized controlled trial (RCT) of a lifestyle intervention in improving physical activity and diet in patients with severe mental disorders (SMD), including schizophrenia, bipolar disorder, and major depressive disorder.	The intervention resulted in significant improvements in physical activity and dietary habits, including increased consumption of fruits and vegetables, and reduced consumption of sugary drinks and fast food. The intervention also led to a decrease in body weight and waist circumference.	401 participants randomized 43.3% with bipolar disorder; 177 (94 in the experimental group and 83 control group) completed the 6-month follow-up.	Moderate	The intervention was effective in improving physical activity and diet in patients with SMD.
Łojko D, Stelmach-Mardas M, Suwalska A. (2018)	Mood Stability, Cognitive Function, and General Health	The review analyzed the relationship between diet and various aspects of bipolar disorder (BD), including mood	Adequate nutrition and dietary patterns may have a positive impact on mood stability, cognitive function, and general health in individuals with BD. BD dietary	N/A (multiple studies included in the review)	Low	Lack of well-designed long-term follow-up studies on BD nutrition strategies

		stability, cognitive function, and general health.	patterns include sugar-rich and high fat products.			
Dorota Łojko, Stelmach-Mardas M, Aleksandra Suwalska. (2019)	Diet Quality and Eating Patterns	The study examined the diet quality and eating patterns in euthymic bipolar patients compared to healthy controls. Four common dietary patterns were identified in BD patients.	Euthymic bipolar patients had significantly lower adherence to the Mediterranean diet and higher consumption of unhealthy foods such as processed meat, sweetened beverages, and fast food compared to healthy controls. Increased values of insulin resistance indicators in the BD group. Mean Mediterranean Diet Score (MDS) in bipolar patients: 28.8 vs. 29.7 in healthy controls, $p<0.05$. Fasting triglycerides (173.4 vs 149.8 $p<.05$), and WC ($p=.026$-$p=.029$ in women and men) were significantly higher in BD group compared to healthy controls. Higher consumption of unhealthy foods in bipolar patients compared to healthy controls: processed meat ($p=0.003$), sweetened beverages ($p<0.001$), and fast food ($p<0.001$).	113 euthymic bipolar patients and 160 healthy controls	Moderate	The study is cross-sectional using a mixture of biochemical data and self-reported data using FFQs
Gabriel FC, Oliveira M, Martella BDM, et al. (2022)	Nutritional factors and BD	The study conducted a systematic review to investigate the association between nutritional factors and Bipolar Disorder (BD).	BD patients with significantly lower serum levels of vitamins A, E, C, folic acid, and PUFAs compared to heathy controls. Meta-analyses of NAC for bipolar disorder suggest improvement in depressive symptoms with moderate effect sizes. Promising applications of CoQ10 supplementation for BD patients. BD patients with higher intake of total daily sucrose, carbohydrates, and intake of sweetened drinks and lower MD scores compared with healthy controls.	N/A (multiple studies included in the review)	Moderate	Mixture of observational and interventional studies, small list of nutrients identified, no intervention trials on whole dietary patterns included
Madireddy S, Madireddy S. (2022)	Mitochondrial function and oxidative stress	The review summarizes current evidence on therapeutic interventions that target mitochondrial dysfunction and oxidative stress in patients with bipolar disorder (BD).	N-acetylcysteine (NAC), omega-3 polyunsaturated fatty acids (PUFAs), and vitamin D have been found to improve mitochondrial function and reduce oxidative stress in BD. Increased uric acid levels during periods of mania and euthymia.	N/A (multiple studies included in the review)	Moderate	Accumulating body of evidence suggests that the therapeutic use of antioxidants in BD is beneficial in the treatment of depression.
Ashton MM, Dean OM, Marx W, et al. (2019)	Response to adjunctive N-acetylcysteine	The study examined the relationship between diet quality, dietary inflammatory	Higher diet quality and lower dietary inflammatory index were associated with better response to adjunctive N-	133 participants randomized:	Moderate	Treatment with the CT and NAC may be optimized if diet quality and body

	and mitochondrial agents in Bipolar Disorder (BD)	index, and body mass index as predictors of response to adjunctive N-acetylcysteine and mitochondrial agents in BD.	acetylcysteine and mitochondrial agents in BD.	n=46 placebo, n=47 NAC only, and n=40 combined treatment (CT)		composition are assessed and improved prior to treatment.
Shah J, Sakshi Gurbani. (2019)	Vitamin D Deficiency Prevalence	The study examined the association between vitamin D deficiency and mood disorders.	The study found that individuals with mood disorders had significantly lower levels of vitamin D compared to those without mood disorders. Additionally, there was a significant negative correlation between vitamin D levels and depressive symptoms.	N/A (multiple studies included in the review)	Low	Limited data specific to patients with bipolar disorder
Jahangard L, Yasrebifar F, Haghighi M, Ranjbar A, Mehrpooya M (2019)	Inflammatory and Oxidative Stress Biomarkers	The study examined the effects of adjuvant Coenzyme Q10 (CoQ10) supplementation on inflammatory and oxidative stress biomarkers in patients with bipolar disorder during the depressive episode.	CoQ10 supplementation led to a significant reduction in serum levels of inflammatory markers such as hs-CRP and IL10, as well as a significant decrease in oxidative stress markers such as TNF-∝, and NO	89 patients; placebo (n=44); CoQ10 (n=45)	Moderate	CoQ10 supplementation showed significant reductions in inflammatory and oxidative stress biomarkers though sample size was small.
Nery FG, Tallman MJ, Cecil KM, et al. (2021)	Depression Symptoms and Glutamate Changes in the Left Prefrontal Cortex	The study investigated the effects of N-acetylcysteine (NAC) on depression symptoms and glutamate changes in the left prefrontal cortex in adolescents and young adults at risk for bipolar disorder.	The study found that NAC treatment was associated with significant reductions in depressive symptoms, as measured by the HAM-D scores, compared to placebo. Additionally, there was a significant increase in glutamate levels in the left prefrontal cortex in the NAC group compared to the placebo group.	9 participants	Low	Evidence was low as sample size was small and the study only included patients at risk for developing BD. NAC may be effective in reducing depressive symptoms and modulating glutamate levels in the left prefrontal cortex in individuals at risk for bipolar disorder.
Wozniak J, DiSalvo M, Farrell A, et al. (2022)	Symptoms of mania and hypomania in pediatric patients	The study investigated the efficacy of N-acetylcysteine (NAC) as a treatment for symptoms of mania and hypomania in pediatric patients with bipolar disorder.	Compared to baseline, participants who received NAC showed significant reductions in Young Mania Rating Scale (YMRS) scores after treatment ≥ 30%	40 participants recruited; only 14 participants (completed all 12 weeks)	Low	High drop-out rate. Preliminary efficacy shown; further research needed.
Porcu M, Urbano MR, Verri WA, et al. (2018)	Depressive Symptoms	The study investigated the effects of adjunctive N-acetylcysteine (NAC) on depressive symptoms in patients with bipolar disorder (BD) and major depressive disorder (MDD) and assessed whether the effects were modulated by baseline high-sensitivity C-reactive protein (hs-CRP) levels.	The study found that NAC treatment was associated with a significant reduction in depressive symptoms in both BD and MDD patients with high hs-CRP levels (>3mg/L). No significant effects were observed in patients with low hs-CRP levels.	67 participants with mixed diagnosis BD and MDD; 25 in the NAC group and 42 in the placebo group. Both groups further divided into CRP levels above or below 3 mg/L	Moderate	Participants with BD and MDD

Davidson M, Rashidi N, Nurgali K, Apostolopoulos V. (2022)	Tryptophan Metabolism	The review summarizes the role of tryptophan metabolites in neuropsychiatric disorders, including major depressive disorder, bipolar disorder, and schizophrenia.	Dysregulation of tryptophan metabolism is implicated in the pathophysiology of neuropsychiatric disorders.	N/A (multiple studies included in the review)	Moderate	Systematic review includes multiple neuropsychiatric disorders.
Huang Y, et al. (2023)	Tryptophan metabolism in central nervous system diseases	The review summarizes the current understanding of tryptophan metabolism in central nervous system diseases, including its role in the pathophysiology of these conditions and potential therapeutic strategies.	Tryptophan metabolism is involved in the pathophysiology of various central nervous system diseases, including BD. Although mechanism of BD is not clearly understood, there is a wide range of evidence that inflammation and TRP metabolism contribute to the development of the disease.	N/A (multiple studies included in the review)	Moderate	Systematic review includes multiple neuropsychiatric disorders.
Evans SJ, Bassis CM, Hein R, et al. (2017)	Gut Microbiome Composition	The study examined the association between gut microbiome composition and bipolar disorder (BD) as well as illness severity. Fecal samples from 115 participants with BD and 64 healthy controls were analyzed using 16S rRNA gene sequencing.	The gut microbiome composition differed significantly between participants with BD and healthy controls. Decreased levels of bacterial taxa, including Faecalibacterium, and Firmicutes were found to be lower in participants with BD and correlated with depressive symptom severity. Composition of the gut microbiome was found to be associated with illness severity in participants with BD.	115 participants with BD and 64 healthy controls	Moderate	The study suggests that gut microbiome composition may be a potential biomarker for BD and illness severity. Further research is needed to confirm these findings and elucidate the underlying mechanisms.
Dickerson F, Adamos M, Katsafanas E, et al. (2018)	Rehospitalization rate	The study investigated the efficacy of adjunctive probiotic microorganisms in influencing rehospitalization rates in patients with acute mania compared to a placebo.	Probiotic treatment also resulted in fewer days rehospitalized (mean 8.3 vs 2.8 days for placebo and probiotic treatment, respectively; $\chi^2 = 5.17$, $P = .017$). Effect of the probiotic treatment on the prevention of rehospitalization was increased in individuals with elevated levels of systemic inflammation at baseline.	33 individuals in the placebo group; 33 individuals in the probiotic treatment group	Moderate	The certainty of evidence is rated as moderate due to the small sample size and limited number of studies. Further research is needed to confirm these findings.
Siwek M, Sowa-Kućma M, Styczeń K, et al.	Serum zinc concentration	The study examined the relationship between serum zinc concentration and depressive episodes in patients with bipolar disorder.	The study found that serum zinc concentration was significantly lower during depressive episodes in patients with bipolar disorder compared to euthymic periods. Increased zinc levels in bipolar individuals experiencing mania also correlated with frequency of manic episodes experienced over one year.	129 participants with BP-1 or BP-2 (58 in depressive episode, 23 in manic episodes, 48 in remission) 50 health volunteers (placebo group)	High	

Jonsson BH, Orhan F, Bruno S, et al. (2021)	Serum Zinc Concentration	The study examined serum zinc concentrations in clinically stable bipolar disorder patients compared to healthy controls.	Serum zinc concentrations were significantly higher in bipolar disorder patients compared to healthy controls. Mean serum zinc concentration: (11.73 ± 0.20 μmol/L, *n* = 121 vs.10.77 ± 0.33 μmol/L, *n* = 30, respectively; *p* = .026)	121 BD patients; 30 healthy controls	High	
Cheng WW, Zhu Q, Zhang HY. (2019)	Chronic Disease Risk BD	The study investigated the association between mineral nutrition and the risk of chronic diseases using Mendelian randomization analysis.	Serum magnesium levels were positively correlated with bipolar disorder, while the opposite was true for serum copper levels. Mg was positively correlated with BD (value = 1.52) . Each 0.16 mmol/L increase in genetically predicted Mg is associated with an 8.74-fold increased risk of BD. Cu was negatively correlated with BD (value = −2.01). A per-unit increase in Cu was associated with a 0.87-fold change in BD risk (p=.01).	For BD, the genetic data is from the newest collection from Psychiatric Genomics Consortium Bipolar Disorder Working Group (PGC-BD). The GWAS analysis was conducted on 20,129 patients and 21,524 controls	High	Results listed here only include those pertaining to BD.
Ciappolino V, DelVecchio G, Prunas C, et al. (2020)	Cognitive Function	The study investigated the effect of DHA supplementation on cognition in patients with bipolar disorder through an exploratory randomized controlled trial.	The DHA group showed significant improvement in verbal fluency and working memory compared to the placebo group. BD patients with placebo had lower GAF scores compared to HCs with (t = 4.1, p = 0.002) or without (t = 4.6, p = 0.0001) Omega 3. HCs also had higher DHA serum levels compared to BD patients. Only the group of HCs receiving 12 weeks of DHA supplementation showed an improvement in cognitive performance in the emotion inhibition test from baseline to follow-up, while the group of BD patients did not show any improvement in any tasks of the neuropsychological battery.	31 BD patients (13 with Omega 3 and 18 with placebo); 21 Healthy Controls (seven with Omega 3 and eight with placebo)	Moderate	Small sample size
Saunders EFH, Mukherjee D, Myers T, et al. (2021)	Mood Stability	The study investigated the preliminary efficacy of a high n-3 plus low n-6 (H3-L6) dietary intervention in	Variability in mood, energy, irritability, and pain as measured using Ecological Momentary Assessment (EMA) was reduced in the H3-L6 group compared	82 participants randomized; 70 completed at	Moderate	Preliminary efficacy shown; further research needed.

		improving mood stability in Bipolar Disorder (BD) compared to a control diet with usual U.S. levels of n-6 and n-3 polyunsaturated fatty acid (PUFA) intakes.	to the control diet (CD) group. No significant differences in mean ratings of mood symptoms, or any other symptom measures, were detected.	least 2 EMA surveys.		
Mitchell ES, Conus N, Kaput J. (2014)	Relationship between B vitamin status and risk of cognitive or behavioral disorders	The review examined the association between B vitamin polymorphisms and various psychiatric and cognitive outcomes.	The review found that certain B vitamin polymorphisms were associated with an increased risk of neurodevelopmental disorders, depression, schizophrenia, bipolar disorder, and cognitive decline. A recent meta-analysis of MTHFR C677T (n = 29,502) researchers found a significant association in schizophrenic and bipolar.	N/A (meta-analysis of multiple studies)	Moderate	Specific polymorphisms and outcomes varied across studies. While many epidemiological studies have shown that B vitamin deficiency is associated with various psychiatric and cognitive issues, B vitamin supplementation has had little effect on its own.
Chmiel I. (2021)	Mood Stability	The paper presents a case report of a patient with bipolar affective disorder who experienced mood stabilization after adopting a ketogenic diet, along with a literature review of studies investigating the use of ketogenic diets in the treatment of bipolar disorder.	The case report describes a patient who experienced improved mood stability and reduced depressive and manic symptoms after adopting a ketogenic diet. The literature review identified several studies suggesting that ketogenic diets may have potential mood-stabilizing effects in bipolar disorder.	1 case report; various numbers of participants in reviewed studies	Low (case report)	Evidence is limited by the small sample size and lack of use of a control.
Dietch DM, Kerr-Gaffney J, Hockey M, et al. (2023)	Mood and Anxiety Improvement	The study conducted a systematic review of the literature to investigate the efficacy of low carbohydrate and ketogenic diets in treating mood and anxiety disorders.	The review found that low carbohydrate and ketogenic diets may have a potential role in improving mood and anxiety symptoms in some individuals with these disorders. However, the evidence is limited by the small number of studies, inconsistent methodology, and lack of long-term follow-up data.	48 studies assessed; 12 studies used in final analysis (varied sample sizes)	Low (due to limitations in the available evidence)	Little research has been conducted to date and no high-grade evidence was found, further studies needed.
Danan A, Westman EC, Saslow LR, Ede G. (2022)	Mood Stability, Reduction in Medication Use	The study analyzed the effects of a ketogenic diet on refractory mental illness in 31 inpatients	Improved mood stability. Mood stability improved Means and standard deviations (SDs) improved for the Hamilton Depression Rating Scale scores from 25.4 (6.3) to 7.7 (4.2), $P < 0.001$ and the Montgomery-Åsberg Depression Rating Scale from 29.6 (7.8) to 10.1 (6.5), $P < 0.001$ Mean (SD) hospitalization length was 85.4 (76.8) days (range 16–270 days)	31 participants; 28 participants followed a ketogenic diet for >2 weeks	Low	Retrospective analysis, small sample size, no control group

			and mean (SD) duration of KD was 59.1 (49.6) days (range 15–248 days) Significant improvements were also observed in metabolic health measures including weight, blood pressure, blood glucose, and triglycerides.			

Conclusions

BD is a complex disease with many factors impacting its development and progression. Based on the multiple studies reviewed, it seems patients with BD would benefit most from a diet high in fat, rich in antioxidants with ample sources of probiotics to support a diverse gut microbiome. In addition, it appears that individuals with BD may benefit from the inclusion of CoQ10, NAC, tryptophan, and adequate food sources containing folate, vitamin B6, vitamin B12, omega-3 fatty acids and vitamin D to prevent micronutrient deficiencies. Although current research on the ketogenic diet for patients with bipolar disorder seems promising, further studies are needed to safely recommend such a diet for this population. Research also indicates that a modified Mediterranean Diet with an emphasis on cardioprotective fat sources may benefit individuals with BD.

Our conclusions may be limited by a dearth of longitudinal studies and randomized controlled trials involving nutrition and BD. Many of the studies on BP and nutrition utilize small sample sizes, especially for studies looking at the effects of the ketogenic diet. In addition, few studies have been conducted on therapeutic, whole dietary patterns interventions (rather than single-nutrient interventions) for patients with bipolar disorder. To date, the ketogenic diet and the Mediterranean Diet are the only two whole dietary patterns studied in this population, although there are likely additional dietary patterns that could prove beneficial. Lastly, to our knowledge, there have been no studies of long-term health outcomes relating to dietary interventions specifically applied to patients with bipolar disorder.

Future studies aimed at investigating whole dietary patterns and taste perception in patients with bipolar disorder may prove beneficial in fully understanding the role of diet for bipolar disorder. Ideally, these would include randomized controlled trials and longitudinal studies aimed at comparing the effects of whole dietary patterns. Although following a therapeutic diet may not lead to full remission, targeted nutrition therapy may play a supportive role with regards to improving treatment response and mitigating symptoms of depression and mania in individuals with BD.

Conflicts of Interest Statement

The authors have no conflicts interest to report.

Funding Statement

The authors received no funding for this project.

References

1. National Institute of Mental Health. BD. www.nimh.nih.gov. Published 2022. https://www.nimh.nih.gov/health/statistics/bipolar-disorder
2. Rowland T, Marwaha S. Epidemiology and risk factors for BD. *Therapeutic Advances in Psychopharmacology*. 2018;8(9):251-269. Doi:https://doi.org/10.1177/2045125318769235
3. Simjanoski M, Patel S, Boni RD, et al. Lifestyle interventions for BDs: A systematic review and meta-analysis. *Neuroscience & Biobehavioral Reviews*. 2023;152:105257. Doi:https://doi.org/10.1016/j.neubiorev.2023.105257
4. Smith DJ, Whitham EA, Ghaemi SN. Chapter 15 - BD. ScienceDirect. Published January 1, 2012. Accessed November 26, 2023. https://www.sciencedirect.com/science/article/abs/pii/B9780444520029000152?via=ihub
5. Solé B, Jiménez E, Torrent C, et al. Cognitive Impairment in BD: Treatment and Prevention Strategies. *International Journal of Neuropsychopharmacology*. 2017;20(8):670-680. Doi:https://doi.org/10.1093/ijnp/pyx032
6. Yatham LN, Kennedy SH, O'Donovan C, et al. Canadian Network for Mood and Anxiety Treatments (CANMAT) guidelines for the management of patients with BD: update 2007. *BDs*. 2006;8(6):721-739. Doi:https://doi.org/10.1111/j.1399-5618.2006.00432.x
7. Lee JG, Woo YS, Park SW, Seog DH, Seo MK, Bahk WM. Neuromolecular Etiology of BD: Possible Therapeutic Targets of Mood Stabilizers. *Clinical Psychopharmacology and Neuroscience*. 2022;20(2):228-239. Doi:https://doi.org/10.9758/cpn.2022.20.2.228
8. Harrison PJ, Geddes JR, Tunbridge EM. The Emerging Neurobiology of BD. *Trends in Neurosciences*. 2018;41(1):18-30. Doi:https://doi.org/10.1016/j.tins.2017.10.006
9. Jones GH, Vecera CM, Pinjari OF, Machado-Vieira R. Inflammatory signaling mechanisms in BD. *Journal of Biomedical Science*. 2021;28(1). Doi:https://doi.org/10.1186/s12929-021-00742-6
10. Luciano M, Sampogna G, Amore M, et al. Improving physical activity and diet in patients with severe mental disorders: Results from the LIFESTYLE multicentric, real-world randomized controlled trial. *Psychiatry Research*. 2022;317:114818. Doi:https://doi.org/10.1016/j.psychres.2022.114818
11. Johnson RJ, Wilson WL, Bland ST, Lanaspa MA. Fructose and uric acid as drivers of a hyperactive foraging response: A clue to behavioral disorders associated with impulsivity or mania? *Evolution and Human Behavior*. Published online October 1, 2020. Doi:https://doi.org/10.1016/j.evolhumbehav.2020.09.006
12. Łojko D, Stelmach-Mardas M, Suwalska A. Is diet important in BD? *Psychiatria Polska*. 2018;52(5):783-795. Doi:https://doi.org/10.12740/pp/onlinefirst/78703
13. Dorota Łojko, Stelmach-Mardas M, Aleksandra Suwalska. Diet quality and eating patterns in euthymic bipolar patients. *PubMed*. 2019;23(3):1221-1238. Doi:https://doi.org/10.26355/eurrev_201902_17016
14. Gabriel FC, Oliveira M, Martella BDM, et al. Nutrition and BD: a systematic review. *Nutritional Neuroscience*. Published online May 24, 2022:1-15. Doi:https://doi.org/10.1080/1028415X.2022.2077031
15. Madireddy S, Madireddy S. Therapeutic Interventions to Mitigate Mitochondrial Dysfunction and Oxidative Stress–Induced Damage in Patients with BD. *International Journal of Molecular Sciences*. 2022;23(3):1844. Doi:https://doi.org/10.3390/ijms23031844
16. Ashton MM, Dean OM, Marx W, et al. Diet quality, dietary inflammatory index and body mass index as predictors of response to adjunctiveN-acetylcysteine and mitochondrial agents in adults with BD: A sub-study of a randomised placebo-controlled trial. *Australian & New Zealand Journal of Psychiatry*. 2019;54(2):159-172. Doi:https://doi.org/10.1177/0004867419882497
17. Shah J, Sakshi Gurbani. *Association of Vitamin D Deficiency and Mood Disorders.*; 2019.
18. Boerman R, Cohen D, Schulte PFJ, Nugter A. Prevalence of Vitamin D Deficiency in Adult Outpatients With BD or Schizophrenia. *Journal of clinical psychopharmacology*. 2016;36(6):588-592. Doi:https://doi.org/10.1097/JCP.0000000000000580
19. Higdon, Ph.D J. Coenzyme Q10 . Linus Pauling Institute: Micronutrient Information Center. Published 2003. 1. Coenzyme Q10. Linus Pauling Institute. Published April 28, 2014.

https://lpi.oregonstate.edu/mic/dietary-factors/coenzyme-Q10

20. Jahangard L, Yasrebifar F, Haghighi M, Ranjbar A, Mehrpooya M. Influence of adjuvant Coenzyme Q10 on inflammatory and oxidative stress biomarkers in patients with BDs during the depressive episode. *Molecular Biology Reports*. Published online July 25, 2019. Doi:https://doi.org/10.1007/s11033-019-04989-z
21. Vasdev S, Singal P, Gill V. The antihypertensive effect of cysteine. *International Journal of Angiology*. 2009;18(01):07-21. Doi:https://doi.org/10.1055/s-0031-1278316
22. Nery FG, Tallman MJ, Cecil KM, et al. N - acetylcysteine for depression and glutamate changes in the left prefrontal cortex in adolescents and young adults at risk for BD: A pilot study. *Early Intervention in Psychiatry*. Published online April 2021. Doi:https://doi.org/10.1111/eip.13149
23. Wozniak J, DiSalvo M, Farrell A, et al. Findings from a pilot open-label trial of N-acetylcysteine for the treatment of pediatric mania and hypomania. *BMC Psychiatry*. 2022;22(1). Doi:https://doi.org/10.1186/s12888-022-03943-x
24. Campbell I, Campbell H. Mechanisms of insulin resistance, mitochondrial dysfunction and the action of the ketogenic diet in BD. Focus on the PI3K/AKT/HIF1-a pathway. *Medical Hypotheses*. 2020;145:110299. Doi:https://doi.org/10.1016/j.mehy.2020.110299
25. Porcu M, Urbano MR, Verri WA, et al. Effects of adjunctive N-acetylcysteine on depressive symptoms: Modulation by baseline high-sensitivity C-reactive protein. *Psychiatry Research*. 2018;263:268-274. Doi:https://doi.org/10.1016/j.psychres.2018.02.056
26. Whitbread D. Top 10 Foods Highest in Tryptophan. myfooddata. Published November 18, 2014. https://www.myfooddata.com/articles/high-tryptophan-foods.php
27. Davidson M, Rashidi N, Nurgali K, Apostolopoulos V. The Role of Tryptophan Metabolites in Neuropsychiatric Disorders. *International Journal of Molecular Sciences*. 2022;23(17):9968. Doi:https://doi.org/10.3390/ijms23179968
28. Huang Y, M.M. Wenxuan Zhao, Chen X, et al. Tryptophan Metabolism in Central Nervous System Diseases: Pathophysiology and Potential Therapeutic Strategies. *Aging and Disease*. 2023;14(3):858-858. Doi:https://doi.org/10.14336/ad.2022.0916
29. Generoso JS, Giridharan VV, Lee J, Macedo D, Barichello T. The role of the microbiota-gut-brain axis in neuropsychiatric disorders. *Braz J Psychiatry*. 2021;43:293-305. http://dx.doi.org/10.1590/1516-4446-2020-0987
30. Rudzki L, Stone TW, Maes M, Misiak B, Samochowiec J, Szulc A. Gut microbiota-derived vitamins - underrated powers of a multipotent ally in psychiatric health and disease. *Progress in Neuro-Psychopharmacology & Biological Psychiatry*. 2021;107:110240. Doi:https://doi.org/10.1016/j.pnpBD.2020.110240
31. Evans SJ, Bassis CM, Hein R, et al. The gut microbiome composition associates with BD and illness severity. *Journal of Psychiatric Research*. 2017;87:23-29. Doi:https://doi.org/10.1016/j.jpsychires.2016.12.007
32. Dickerson F, Adamos M, Katsafanas E, et al. Adjunctive probiotic microorganisms to prevent rehospitalization in patients with acute mania: A randomized controlled trial. *BDs*. 2018;20(7):614-621. Doi:https://doi.org/10.1111/bdi.12652
33. Douglas LC, Sanders ME. Probiotics and Prebiotics in Dietetics Practice. *Journal of the American Dietetic Association*. 2008; 108(3):510-521. Doi:https://doi.org/10.1016/j.jada.2007.12.009
34. Siwek M, Sowa-Kućma M, Styczeń K, et al. Decreased serum zinc concentration during depressive episodes in patients with BD. *Journal of Affective Disorders*. 2016;190:272-277. Doi:https://doi.org/10.1016/j.jad.2015.10.026
35. Jonsson BH, Orhan F, Bruno S, et al. Serum concentration of zinc is elevated in clinically stable BD patients. *Brain and Behavior*. 2021;12(1). Doi:https://doi.org/10.1002/brb3.2472
36. Cheng WW, Zhu Q, Zhang HY. Mineral Nutrition and the Risk of Chronic Diseases: A Mendelian Randomization Study. *Nutrients*. 2019;11(2):378. Doi:https://doi.org/10.3390/nu11020378
37. Ciappolino V, DelVecchio G, Prunas C, et al. The Effect of DHA Supplementation on Cognition in Patients with BD: An Exploratory Randomized Control Trial. *Nutrients*. 2020;12(3):708. Doi:https://doi.org/10.3390/nu12030708
38. Saunders EFH, Mukherjee D, Myers T, et al. Adjunctive dietary intervention for BD: a

randomized, controlled, parallel-group, modified double-blinded trial of a high n-3 plus low n-6 diet. *BDs*. Published online August 2, 2021. Doi:https://doi.org/10.1111/bdi.13112

39. Harvard T.H. Chan School of Public Health. Omega-3 Fatty Acids: An Essential Contribution. The Nutrition Source. Published May 22, 2019. https://www.hsph.harvard.edu/nutritionsource/what-should-you-eat/fats-and-cholesterol/types-of-fat/omega-3-fats/
40. Mitchell ES, Conus N, Kaput J. B vitamin polymorphisms and behavior: Evidence of associations with neurodevelopment, depression, schizophrenia, BD and cognitive decline. *Neuroscience & Biobehavioral Reviews*. 2014;47:307-320. Doi:https://doi.org/10.1016/j.neubiorev.2014.08.006
41. Harvard School of Public Health. B Vitamins. The Nutrition Source. Published June 4, 2019. https://www.hsph.harvard.edu/nutritionsource/vitamins/vitamin-b/
42. Chmiel I. Ketogenic diet in therapy of bipolar affective disorder - case report and literature review. *Psychiatria Polska*. Published online July 19, 2021:1-19. Doi:https://doi.org/10.12740/pp/onlinefirst/136356
43. Kuang H, Duong A, Jeong H, Zachos K, Andreazza AC. Lactate in BD: A systematic review and meta-analysis. *Psychiatry and Clinical Neurosciences*. 2018;72(8):546-555. Doi:https://doi.org/10.1111/pcn.12671
44. Li X, Yang Y, Zhang B, et al. Lactate metabolism in human health and disease. *Signal Transduction and Targeted Therapy*. 2022;7(1):1-22. Doi:https://doi.org/10.1038/s41392-022-01151-3
45. Dietch DM, Kerr-Gaffney J, Hockey M, et al. Efficacy of low carbohydrate and ketogenic diets in treating mood and anxiety disorders: systematic review and implications for clinical practice. *BJPsych Open*. 2023;9(3):e70. Doi:https://doi.org/10.1192/bjo.2023.36
46. Danan A, Westman EC, Saslow LR, Ede G. The Ketogenic Diet for Refractory Mental Illness: A Retrospective Analysis of 31 Inpatients. *Frontiers in Psychiatry*. 2022;13. Doi:https://doi.org/10.3389/fpsyt.2022.951376a