Nutrient-Based Therapies for Bipolar Disorder: A Systematic Review

Louisa G. Sylvia\textsuperscript{a, b}, Amy T. Peters\textsuperscript{a} Thilo Deckersbach\textsuperscript{a, b} Andrew A. Nierenberg\textsuperscript{a, b}

\textsuperscript{a}Bipolar Clinic and Research Program, Massachusetts General Hospital, and \textsuperscript{b}Harvard Medical School, Boston, Mass., USA

Abstract

Background: Pharmacotherapy is the first line of treatment for bipolar disorder, but many patients continue to experience persistent subthreshold symptoms. Alternative adjunct treatments, including nutritional therapies, may have the potential to alleviate residual symptoms and improve the outcomes of standard pharmacotherapy. The aim of this paper is to critically review the current clinical evidence and mechanisms of action of nutrient-based therapies alone or in combination with commonly used pharmacotherapies for mania and bipolar depression. Methods: We conducted a Medline search for clinical trials conducted with humans, published in English from 1960 to 2012 using nutritional supplements such as n–3, chromium, inositol, choline, magnesium, folate and tryptophan alone or in combination with pharmacotherapies for the treatment of bipolar disorder. Results: Preliminary data yields conflicting but mainly positive evidence for the use of n–3 fatty acids and chromium in the treatment of bipolar depression. Limited evidence found that inositol may be helpful for bipolar depression, but larger sample sizes are needed. Preliminary randomized, controlled trials suggest that choline, magnesium, folate and tryptophan may be beneficial for reducing symptoms of mania. Conclusions: Given the potential public health impact of identifying adjunct treatments that improve psychiatric as well as physical health outcomes, nutritional treatments appear promising for the management of bipolar disorder but require further study.

Key Words

Bipolar disorder • Nutrient-based therapy • Alternative treatments

Introduction

Pharmacotherapy is the foundation of treatment for bipolar disorder. Nevertheless, even with successful treatment, 54–68% of individuals continue to experience subthreshold symptoms [1]. Additionally, between 20 and 60% have adverse side effects that make it difficult for patients to tolerate taking these medications [2–4]. Even with sufficient adherence, up to 60% experience recurrent manic or depressive mood episodes [5]. Because of these limitations, it is important to identify alternative or complementary treatments that are not only successful in the management of residual symptoms, but also well tolerated and acceptable to patients.

Broadly, nutritional supplementation in psychiatry has some evidence that it can improve selected residual
and nutritional habits and overall physical health. For example, in the general population, the important role of essential fatty acids in the diet and perhaps given as supplements in maintaining physical health is well established [6]. Amongst other health benefits, essential fatty acids have anti-inflammatory, antithrombotic, antiarrhythmic and lipid-lowering effects [6] that aid the prevention and treatment of physical illnesses ranging from coronary heart disease [7] to rheumatoid arthritis [8]. More recently, there has been increasing evidence that essential fatty acids are important not only for physical health, but also for brain development and function [9–11]. As a result, there has been increasing interest in the use of essential fatty acids for the treatment of psychiatric disorders. Essential fatty acids and their eicosanoid derivatives are important constituents of the brain and regulators of neuronal function. Abnormal biochemistry of essential fatty acids, impaired fatty acid-related signal transduction processes, and impaired phospholipid metabolism are associated with psychiatric disorders [12–15]. Reduced levels of membrane essential polyunsaturated fatty acids and increased levels of lipid peroxidation products are associated with schizophrenia [15]. Patients with anorexia nervosa demonstrate deficiencies of selected essential fatty acids, compensatory changes in nonessential fatty acids and decreased fluidity of plasma lipids that are different from simple nutritional essential fatty acid deficiency or chronic malnutrition [16]. Deficits of n–3 polyunsaturated fatty acids are associated with alcohol [17, 18] and polysubstance abuse [14]. And finally, decreased levels of most n–3 polyunsaturated fatty acids have been found in the red blood cell membranes of patients with social anxiety disorder [19] as well as in those with mood disorders [12, 20]. Investigators such as Horrobin, Buydens-Branchez, and their colleagues [13, 14, 20–22] have demonstrated that supplementation of these essential fatty acids may help to improve outcomes across several domains of psychopathology, including aggression.

Consequently, nutritional supplementation of pharmacotherapy may be particularly appealing for the treatment of bipolar disorder, not only for improving residual psychiatric symptoms, but also for improving physical health. Bipolar disorder is associated with poor eating and nutritional habits [23, 24] and increased risk of obesity [25]. Individuals with bipolar disorder tend to cook fewer than two meals per day, consume more carbohydrates, sucrose and sugared beverages, and report having difficulty obtaining or cooking food. These behaviors increase the likelihood that they will consume unhealthy prepackaged or prepared food without essential vitamins, minerals and n–3 fatty acids [26] and with significantly lower levels of the essential nutrients thiamin, riboflavin, folate, phosphorus, zinc, vitamin B₆ and vitamin B₁₂ compared to population norms [27]. Early pilot research in this domain by Cohen et al. [28] suggested that the use of lecithin may have the potential to improve symptoms of mania. The aim of this paper is to critically review the current clinical evidence and mechanisms of action of nutrient-based therapies alone or in combination with commonly used pharmacotherapies for mania and bipolar depression.

**Methods**

Studies included in this review were identified and reported in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses [29]. We conducted a Medline search for clinical trials in humans published in English of nutritional therapies for bipolar disorder using the search terms: *bipolar disorder, bipolar mania, bipolar depression, mania, hypomania, and cyclothymia*, along with nutritional supplementation-relevant terms such as *nutritional supplement, nutraceuticals, nutrient-based therapy, essential fatty acids, omega-3, chromium, inositol, choline, magnesium, folate and tryptophan*. We identified 23 relevant articles published from 1960 to 2011. Criteria for inclusion in this review consisted of either open-label or controlled human studies of nutrient-based supplements used alone or adjunctively with existing medication for participants diagnosed with bipolar disorder, subtype I or II according to DSM-III or -IV criteria [30, 31]. Studies included must have used measured outcomes on established psychiatric scales, a sample size ≥5 (online suppl. fig. 1, table 1; for all online supplementary material, see www.karger.com/doi/10.1159/000341309), and no identifiable conflict of interest.

**Results**

The methods of studies included in this review are summarized in online supplementary table 1. Unless otherwise noted, all studies were conducted in outpatient settings with adults (age ≥17 years), and most dietary supplements were added to treatment as usual for bipolar disorder. No sources of conflict of interest were identified for any of the included studies (online suppl. table 2) [32].

### n–3 Fatty Acids

One of the most studied nutritional supplements for bipolar disorder are the n–3 fatty acids [33]. n–3 fatty acids dampen signal transduction pathways associated with phosphatidylinositol and arachidonic acid, suppress
Table 1. Mechanisms and preliminary clinical benefits of nutrient-based therapies in bipolar disorder

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Mechanism</th>
<th>Benefit</th>
</tr>
</thead>
<tbody>
<tr>
<td>n–3 fatty acids</td>
<td>Dampens overactivity of cell signal transduction pathways</td>
<td>Improves depression</td>
</tr>
<tr>
<td>Inositol</td>
<td>Controls intracellular calcium concentration and modulates serotonin activity</td>
<td>Improves depression, reduces lithium-induced psoriasis</td>
</tr>
<tr>
<td>Choline</td>
<td>Modifies high-energy phosphate metabolism</td>
<td>Improves mania in rapid cycling bipolar disorder</td>
</tr>
<tr>
<td>Magnesium</td>
<td>Facilitates conversion of 5-hydroxytryptophan into serotonin</td>
<td>Improves agitation and mania</td>
</tr>
<tr>
<td>Chromium</td>
<td>Metabolizes glucose and fat, produces neurotransmitters</td>
<td>Improves atypical depression</td>
</tr>
<tr>
<td>Folate</td>
<td>Produces S-adenosylmethionine and healthy red blood cells</td>
<td>Improves depression</td>
</tr>
<tr>
<td>Tryptophan</td>
<td>Reduction in plasma tryptophan produces a consequent reduction in brain serotonin synthesis and release</td>
<td>Improves mania</td>
</tr>
</tbody>
</table>

eicosanoid-mediated inflammatory processes, increase membrane fluidity, modulate ion channel and receptor activity, and activate nuclear receptor effects [34–36]. n–3 fatty acids have potential therapeutic effects in bipolar disorder by targeting cell signal transduction over activity, eicosanoid-mediated inflammatory processes, membrane rigidity, and suppressed activity of nuclear receptors [36]. The 2 n–3 fatty acids in fish oil are eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA) [37].

In a preliminary prophylaxis trial by Stoll et al. [38], n–3 fatty acids were well tolerated and improved the short-term course of bipolar illness. During this 4-month study, patients with bipolar I or II disorder were randomized to adjunctive treatment with high doses of fish oil (9.6 g/day of DHA plus EPA; n = 14) or placebo (olive oil; n = 16). Patients randomized to the fish oil demonstrated significantly longer remissions and greater improvements of depressive symptoms (Hamilton Depression Scale mean decrease = 3.3 points more than placebo with a Cohen’s d = 0.34) as well as global illness impressions (Clinical Global Impression mean decrease = 0.79 more than placebo). No differences in manic symptoms were noted. There was no apparent benefit of 2 g over the 1 g dose of daily ethyl-EPA. By contrast, a 4-month, randomized, placebo-controlled trial found no benefit of adjunctive ethyl-EPA 6 g/day over placebo in the treatment of outpatients with bipolar depression (n = 59) or rapid cycling (n = 62) [40]. Another small randomized controlled trial (n = 15) of adjunctive EPA plus DHA in the treatment of acute mania found no benefit over placebo in reducing mania [41].

Additional data from 4 small, open-label trials (table 1) suggest that adjunctive n–3 fatty acids may help reduce symptoms of depression and irritability in adults with bipolar disorder [42, 43], and manic and depressive symptoms in children and adolescents with pediatric bipolar disorder [44]. Wozniak et al. [45] found that monotherapy with EPA plus DHA was associated with modest improvements in manic symptoms in an 8-week study for pediatric bipolar disorder. The results of a randomized, double-blind, placebo-controlled pilot study of DHA for medication-free patients (n = 10) suggest that, although results of the trial are not sufficient to support a recommendation of monotherapy treatment as a substitute for standard pharmacological treatments, DHA was well tolerated and a larger study of monotherapy would be feasible [46]. However, a previous 16-week randomized controlled trial of n–3 augmentation for pediatric (ages 6–17 years) bipolar disorder demonstrated that flax oil containing ALA (a dietary precursor of n–3 fatty acids with inefficient conversion to EPA and DHA) as adjunctive treatment or monotherapy did not demonstrate better mood stabilization than placebo (olive oil) in patients with bipolar I or II disorder (n = 51) [47].

Overall, while some data suggests that EPA and DHA may have some efficacy in bipolar disorder, the results are mixed and far from definitive.

**Inositol**

Inositol is a constituent of the intracellular phosphatidylinositol second-messenger system, which is linked to...
various neurotransmitter receptors. Inositol crosses the blood-brain barrier in pharmacological doses, and has shown efficacy in a small study of unipolar depression [48] as well as a few studies in bipolar depression.

The largest controlled trial of inositol for treatment-resistant bipolar depression randomized 66 patients to lamotrigine, inositol or risperidone added to ongoing mood stabilizer treatment [49]. The overall recovery rates were 23.8% (95% CI, 5.8–41.8) for lamotrigine, 17.4% (95% CI, 2.4–32.4) for inositol, and 4.6% (95% CI, 0–14.6) for risperidone. Although no statistically significant difference was found between the three treatments with the limited sample size, enough patients treated with lamotrigine and inositol reached recovery to suggest that further investigation of inositol, with larger samples, may be warranted.

Two subsequent double-blind, placebo-controlled trials of adjunctive inositol yielded conflicting results. One study randomized adults with bipolar depression (n = 24) to either 12 g of inositol or placebo (D-glucose) for 6 weeks [50]. Therapeutic levels of medications (lithium, valproate, carbamazepine) at study entry were continued unchanged. Participants receiving inositol had at least a 50% improvement in depressive symptoms, as well as significant improvements in their global illness severity, compared to patients receiving placebo (Cohen’s d = 0.36). In contrast, a randomized trial of 17 depressed individuals with bipolar disorder, taking therapeutic levels of lithium or valproate for at least 2 weeks, were assigned to receive double-blind inositol or placebo for 6 weeks [51]. Results indicated a trend for more subjects on inositol to show improvement in depressive symptoms, but inositol was not shown to be more effective than placebo.

Choline
Choline administration has been reported to increase brain phosphatidylcholine levels [52]. Phospholipid synthesis for maintaining membrane integrity in brain cells consumes approximately 10–15% of the total adenosine triphosphate, therefore an increased availability of brain choline may lead to an increase in adenosine triphosphate consumption [53]. Choline supplementation may play a role in the course of the disorder by modifying high-energy phosphate metabolism given that dysfunction in mitochondria [54–56] and phosphate metabolism is observed in bipolar disorder [57–60].

A 12-week, randomized, placebo-controlled (n = 44) trial of adjunct choline was conducted in outpatients with a history of mania or hypomania and cocaine dependence [61]. The use of choline was associated with improvement relative to placebo in declarative memory and cocaine use, but not symptoms of mania or depression. A smaller, randomized trial of lithium-treated patients with rapid cycling bipolar disorder (n = 8) assigned patients to adjunctive treatment with choline or placebo for 12 weeks [52]. There were no statistically significant differences in symptoms of mania or depression, although the choline treatment group demonstrated a significant decrease in purine metabolite ratios which may contribute to the antimanic action of choline by regulating mitochondrial dysfunction.

An open pilot trial, however, does suggest a potential benefit of choline on mood. Stoll and colleagues [62] examined choline augmentation in rapid-cycling bipolar disorder treated with lithium. Five of the 6 rapid-cycling patients had a substantial reduction in manic symptoms, and 4 patients had a marked reduction in manic and depressive symptoms during choline therapy. Choline was well tolerated in all cases and an effective treatment for 4 (66.7%) of the rapid-cycling patients.

Magnesium
Magnesium deficiency is common and appears to negatively impact mood in the general population [63]. Magnesium is second only to potassium in intracellular concentration and facilitates the conversion of 5-hydroxytryptophan into serotonin. Similar to the mechanism of action of some drug treatments for mood disorders (such as the protein kinase C inhibitors lithium, valproate, tamoxifen, and lamotrigine), magnesium is associated with changes in monoaminergic neurotransmission. Magnesium is also a noncompetitive N-methyl-D-aspartate antagonist and alters protein kinase C activity [64–66]. Signs of magnesium deficiency include fatigue, irritability, insomnia, loss of appetite, mental confusion and a vulnerability to stress [67, 68].

A few reports suggest that magnesium can exert antimanic effects. One randomized study (n = 20) compared magnesium oxide augmentation to placebo in acutely manic patients pretreated with verapamil (an L-type calcium channel blocker of the phenylalkylamine class) shown to demonstrate antimanic effects [69]) over 18 weeks [70]. Magnesium oxide successfully induced higher levels of serum magnesium and was significantly more effective than placebo in reducing manic symptoms (on the Brief Psychiatric Rating Scale). A smaller, open trial of individuals (n = 10) with treatment-resistant mania were treated with injections of magnesium sulfate (adjunctive to lithium, haloperidol, clonazepam) for up to 3 weeks [71]. Seven out of 10 patients demonstrated a marked improvement in global illness severity.
The only study to the best of our knowledge using magnesium monotherapy (40 mEq/day) found that magnesium reduced symptoms of mania in rapid-cycling patients (n = 9) [72]. These pilot studies suggest that magnesium may be a useful supplementary therapy for the clinical management of mania, but further research is necessary.

Chromium
The dietary trace mineral chromium acts on monoamine neurotransmitter systems and plays a crucial role in glucose and fat metabolism [73, 74]. Chromium improves insulin sensitivity in the hypothalamus, which enhances hypothalamic function by increasing glucose use in the central nervous system. Enhanced hypothalamic function may lead to an increased synthesis of serotonin, norepinephrine and melatonin [75]. Given evidence that patients with depression use less glucose [76], increased synthesis of these neurotransmitters may help to improve mood in patients with depression.

Three pilot trials of chromium indicate an antidepressant effect in patients with unipolar depression when used as adjunctive or monotherapy [77–79]; however, a randomized placebo-controlled investigation of chromium in patients experiencing atypical depression (n = 113) showed no significant difference in depressive symptoms between the groups. The only published trial of chromium use in bipolar disorder evaluated open-label adjunctive chromium for treatment-resistant, rapid-cycling bipolar disorder (n = 30) over the course of 2 years [80]. Approximately one third of patients experienced a reduction in depressive symptoms; however, participant dropout rates were high. The long-term benefit of chromium for the treatment of bipolar disorder warrants further investigation, particularly its tolerability given the high attrition rates.

Vitamin B, Folic Acid
Adequate levels of folate are essential for proper brain functioning [81]. Folate, with vitamins B₁₂ and B₆ as catalyzing cofactors, influences cognitive performance and mood [82–86]. Several reports indicate a high prevalence of folic acid deficiency among patients suffering from psychiatric conditions such as depression, bipolar disorder and cognitive dysfunction disorders [83, 87–90].

Behzadi et al. [91] conducted a preliminary randomized controlled trial (n = 88) of folic acid added to sodium valproate for 3 weeks to treat acute mania. Patients experienced greater improvement with adjunct folic acid, such that symptoms of mania (language, thought disorder, irritability and disruptive-aggressive behavior) improved. This is the only published trial of adjunctive folic acid in bipolar disorder, but evidence suggests that reduced red cell folate in mania is associated with bipolar illness [92]. Such deficiencies, however, seem greatest in a depressive state [93], consistent with several previous trials that have demonstrated efficacy of folic acid in the treatment of unipolar depression [94]. For example, a 6-month trial of 24 patients with depression and folate deficiency (red blood cell folate level <200 μg/l), 15 mg/day of L-methylfolate or placebo was added to existing treatment with antidepressant medication. A small but significant improvement was noted in depressive symptoms [83]. In a larger sample (n = 127) of unipolar depressed patients treated with fluoxetine and 0.5 mg of folic acid daily for 10 weeks, depressive symptoms (i.e. Hamilton Rating Scale for Depression) improved compared to the folate group [95]. These data in unipolar samples suggest that folic acid may be beneficial for individuals with bipolar disorder.

Rapid Tryptophan Depletion
Serotonin is known to play an important role in a wide variety of functions, including mood, anxiety, aggression, sleep, appetite and sexual function. The aim of rapid tryptophan depletion is to lower brain serotonin by depleting the amino acid precursor tryptophan. The rapid tryptophan depletion paradigm is based on the hypothesis that reducing plasma tryptophan produces a consequent reduction in brain serotonin synthesis and release [96]. Rapid reduction of up to 80% in plasma tryptophan levels can be accomplished with administration of an oral tryptophan-free amino acid solution, which induces hepatic protein synthesis and thereby depletes available plasma tryptophan. Findings that tryptophan depletion produces a relapse of symptoms in treated depression suggest that enhanced serotonin function is important in maintaining response to antidepressants [97–101].

Rapid tryptophan depletion has been studied as a potential antimanic agent in acutely manic patients. It is approved as adjunctive medication to lithium in bipolar disorder in Canada; however, the double-blind placebo controlled study conducted in 1985 which led to its approval is not published [102]. Of the published studies assessing its efficacy in bipolar disorder, one double-blind, placebo-controlled pilot study of rapid tryptophan depletion for acute mania randomized participants (n = 23) to receive 7 days of a daily tryptophan-free amino acid drink or a placebo drink. Individuals who consumed the amino acid...
acid drink experienced greater improvement in manic symptoms and global illness impressions compared to the control group, suggesting that rapid tryptophan depletion may have an antimanic effect. The rate of intolerance, however, was high with 5 (23%) participants in the treatment group dropping out of the study; the results are from those patients who were able to tolerate the drink [103]. An additional 2-week study using 12 g of the amino acid L-tryptophan in 24 participants with mania also found potential benefits for reducing mania. The 2-phase trial found that mania severity was significantly reduced with L-tryptophan on the Clinical Global Inventory in the initial open phase and continued but lessened during the controlled phase [104]. Despite L-tryptophan’s promising antimanic effects, the amino acid nutritional supplement has been banned by the Food and Drug Administration since 1989 due to a rare and deadly flu-like condition (eosinophilia-myalgia syndrome) associated with its use [105, 106].

**Discussion**

The addition of nutritional supplements to first-line pharmacological therapies for bipolar disorder may have potential synergistic pharmacodynamic effects. Specifically, it is possible that the combination of nutritional supplements and psychiatric drugs may provide an additive effect that is greater than the sum of the two treatments’ independent effects. Studies investigating the mechanism of action of nutrient-based supplements have demonstrated that their combination with pharmacotherapies can provide benefit beyond the effect of their isolated treatment [107]. Thus, we summarize the current hypothesized mechanism of action of nutrient-based therapies, clinical implications of these data for bipolar disorder, and critical areas for future research.

The most extensively studied nutritional supplement in bipolar disorder is n–3 fatty acids. While preliminary studies have demonstrated inconsistent outcomes, overall adjunctive n–3 fatty acids could potentially reduce symptoms of bipolar depression in adults (online suppl. table 1). However, future research is needed to explore the long-term benefit of n–3 fatty acids as well as the antimanic and antidepressant efficacy of augmentation and monotherapy in children and adolescents.

Preliminary research of inositol and choline suggests a possible efficacy. Adjunctive inositol is associated with modest improvements in depressive symptoms as well as reductions in side effects, which is consistent with data from unipolar samples [26]. Larger placebo-controlled studies, however, are needed to confirm the potential efficacy of inositol in the treatment of bipolar depression. Results from several small pilot studies also indicate that choline is well tolerated and appears to have antimanic efficacy in rapid-cycling patients. Magnesium supplementation is also successful in reducing symptoms of mania, and may have benefit as monotherapy in rapid-cycling patients.

Based on data in unipolar depression, the first trials of chromium and folate in bipolar disorder indicate that increasing levels of chromium and folate may have beneficial effects on mood. The sample size in the study of chromium, however, was small, and there was a high dropout rate. Thus, while increased intake of chromium may improve outcomes, future research is needed to determine the tolerability and efficacy of chromium in a larger sample. Folate augmentation in bipolar disorder was associated with a decrease in mania symptoms, but may also be beneficial in treating depressive symptoms since low levels of folate are associated with mania and depression. Future trials should focus on the efficacy of folate in the treatment of bipolar depression as well as replicate the promising pilot data of its efficacy in treating mania.

The current evidence for the efficacy of nutritional supplements for bipolar disorder is associated with several limitations. First, the sample sizes for most studies are small, limiting the generalizability of the results. These studies also tended to use open label designs which can introduce rater bias and enhance the likelihood of observing a placebo response. The dosing of these dietary supplements is also unclear as randomized, controlled trials have not adequately compared the efficacy of various doses. Additionally, the results of these studies focus largely on clinical outcomes, which, while valuable, do not address the potential role of nutritional supplementation in improving health outcomes. Furthermore, conflict of interest should be considered in the interpretation of these results. Although none of these studies were funded exclusively by product developers, a select number of trials included in this review were provided the nutritional supplement by the product manufacturers. Therefore, in sum, these data should be interpreted with caution, such that they may be used primarily to generate future research opposed to offering confirmatory guidelines. Despite these limitations, the preliminary evidence in bipolar disorder is promising, particularly given the benefits observed in other clinical populations (e.g. unipolar depression) [26].
A key area of future research is identifying how these data on nutrient-based supplements may inform potential dietary changes. This is particularly relevant for individuals with bipolar disorder given that they tend to have poor diets compared to healthy controls [24]. It is also possible that the relationship of diet and psychiatric illness is bidirectional. For example, an exploratory analysis of women with bipolar disorder (n = 23) compared to a control cohort (n = 691), found that Western or modern diets (diets higher in refined sugars, process foods and fats) were associated with an increased risk of bipolar disorder [108]. This relationship is further supported by data that Western diets are associated with a higher risk of ischemic heart disease [109] and lower brain-derived neurotropic factor [110], both potential risk factors of bipolar disorder [111]. In contrast, traditional Mediterranean diets which are higher in nutrient-rich foods (e.g. vegetables, fruits, legumes, whole grains and olive oil) are associated with a lower risk of heart disease [58] and are less correlated with depression and anxiety [112–114]. Moreover, a recent study in a sample of women (n = 1,046) found that reduced intake of red meat was associated with diagnoses of depressive or anxiety disorders [115]. Thus, individuals with mood disorders tend to have poor diets which may lead to nutritional deficiencies and, likewise, individuals with poor diets may be at increased risk for developing psychiatric illness.

These data highlight the importance of healthy eating and how this may improve the course of psychiatric illness and potentially, buffer against their onset. This is particularly relevant for individuals with bipolar disorder who tend to have a sedentary lifestyle, which increases their morbidity and mortality [116]. Exercise improves a number of important risk factors, such as cardiorespiratory fitness, weight, high-density lipoprotein cholesterol level, and fasting insulin level [117, 118] and has been associated with improvements in mood and functioning [119]. Thus, adjunct exercise has the dual potential to substantially improve acute and long-term health and psychiatric outcomes for patients with bipolar disorder [119]. Psychosocial interventions adjunctive to pharmacotherapy help to improve a number of psychiatric outcomes [120, 121] and could enhance both psychiatric and physical outcomes by incorporating health and wellness teaching. Indeed, in a pilot study of an integrated psychosocial intervention addressing nutrition, weight loss, exercise and wellness in bipolar disorder, participants demonstrated improvements in quality of life, depressive symptoms and weight [122]. Additionally, given the bidirectional relationship between exercise and nutrition, future research could investigate the effects of psychological interventions that focus on the importance of physical and mental well-being, in combination with nutrient-based therapies. These alternative strategies may be particularly appealing for the treatment of cyclothymic disorder, characterized by mild or moderate fluctuations in mood. The use of antidepressants and mood stabilizers for treatment of cyclothymic disorder is understudied in the clinical trial literature [123]; however, preliminary psychosocial intervention research suggests that a combination of cognitive behavioral and well-being therapy improves mood [124].

In summary, the existing data indicate that future research on the efficacy of dietary supplements and additional alternative treatments for the maintenance of bipolar disorder is warranted. In particular, given the potential public health impact of identifying adjunct treatments that improve psychiatric as well as physical health outcomes, nutritional supplementation may become a valuable tool in managing an illness with a chronic course.

References


Nutrient-Based Therapies for Bipolar Disorder


32 Fava GA: Unmasking special interest groups: the key to addressing conflicts of interest in medicine. Psychother Psychosom 2010;79:203–207.


55 Andreazza AC, Shao L, Wang JF, Young LT: Mitochondrial complex I activity and oxidative damage to mitochondrial proteins in the prefrontal cortex of patients with bipolar disorder. Arch Gen Psychiatry 2010;67:360–368.


66 Zarate CA, Manji HK: Protein kinase C inhibition: rationale for use and potential in the treatment of bipolar disorder. CNS Drugs 2009;23:569–582.


Sylvia/Peters/Deckersbach/Nierenberg
Nutrient-Based Therapies for Bipolar Disorder
