

## Review Article

## Adjunctive nutraceuticals with standard pharmacotherapies in bipolar disorder: a systematic review of clinical trials

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**Objective:** Studies using augmentation of pharmacotherapies with nutraceuticals in bipolar disorder (BD) have been conducted and preliminary evidence in many cases appears positive. To date, however, no specialized systematic review of this area has been conducted. We present the first systematic review of clinical trials using nutrient-based nutraceuticals in combination with standard pharmacotherapies to treat BD. A subsequent aim of this report was to discuss posited underlying mechanisms of action.

**Methods:** PubMed, CINAHL, Web of Science, and Cochrane Library databases, and grey literature were searched during mid-2010 for human clinical trials in English using nutraceuticals such as omega-3, N-acetyl cysteine (NAC), inositol, and vitamins and minerals, in combination with pharmacotherapies to treat bipolar mania and bipolar depression. A review of the results including an effect size analysis (Cohen's *d*) was subsequently conducted.

**Results:** In treating bipolar depression, positive evidence with large effect sizes were found for NAC ( $d = 1.04$ ) and a chelated mineral and vitamin formula ( $d = 1.70$ ). On the outcome of bipolar mania, several nutraceuticals reduced mania with strong clinical effects: a chelated mineral formula ( $d = 0.83$ ), L-tryptophan ( $d = 1.47$ ), magnesium ( $d = 1.44$ ), folic acid ( $d = 0.40$ ), and branched-chain amino acids ( $d = 1.60$ ). Mixed, but mainly positive, evidence was found for omega-3 for bipolar depression, while no evidentiary support was found for use in mania. No significant effect on BD outcome scales was found for inositol (possibly due to small samples).

**Conclusions:** BD treatment outcomes may potentially be improved by additional use of certain nutraceuticals with conventional pharmacotherapies. However, caution should be extended in interpreting the large effects of several isolated studies, as they have not yet been replicated in larger trials.

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It is estimated that two-thirds of individuals diagnosed with bipolar disorder (BD) are moderately to severely ill in any given year (1), with fewer than half of patients who take conventional pharmacotherapies following an initial manic episode reporting a

sustained control of symptoms (2). Furthermore, up to 60% of BD patients who adhere to pharmacological treatment experience recurring manic or depressive mood episodes while taking medications at recommended therapeutic doses (3). Due to these considerations adjunctive strategies are often employed to improve clinical outcomes. Adjunctive treatment with conventional pharmacotherapies

Disclosure information for all authors is listed before the references.

can be classed as *augmentation* or *combination* approaches (4). Prescriptive augmentation involves using psychotropic interventions that are not recognized monotherapies in conjunction with pharmaceutical medicines in order to improve clinical response or mitigate side-effects. Combination strategies often involve using two or more established pharmaceutical medications for the same purpose. Adjunctive strategies can be initiated either at the beginning of the prescription to potentially increase chance of response or later after partial or non-response to medication.

One potential form of adjunctive treatment with standard pharmacotherapies involves the use of nutraceuticals. A *nutraceutical* has been defined as any substance which is considered a food, a part of a food, a vitamin, a mineral, or a herb that provides health benefits (5). While some *nutrient* nutraceuticals (e.g., amino acid or omega-3 formulations) may have efficacy as monotherapies, their role may be greater in augmenting the action of mood stabilizers, antipsychotics, or antidepressants, which are primary treatments for BD (6, 7). Aside from potentially increasing the clinical response and efficacy of conventional medicines, the use of specific adjunctive nutraceuticals in BD may allow for smaller doses of mood stabilizers or atypical antipsychotics to be administered, as was demonstrated by Kaplan et al. (8) who reported a > 50% reduction of medication usage while using an adjunctive mineral and vitamin formula. While this could potentially ameliorate typical side effects, increasing adherence, and improve overall outcomes, currently there is no substantive evidence supporting this effect.

Pharmacodynamic effects of nutraceuticals on mood are posited to be underpinned by a number of mechanisms. These include a modulation of epigenetics or methylation pathways, increased enzymatic catabolism of neurochemicals, or modification of membrane receptor/channel/secondary messenger communication (9, 10). Examples of potential effects of combining nutrients with pharmacotherapies in BD include: amino acid administration (or depletion regimes) modifying dopamine or serotonin synthesis (11, 12); anti-inflammation, modulation of cell signal transduction, and phosphoinositide (PI)-protein kinase C antagonism from essential fatty acids (13–16); N-methyl-D-aspartate (NMDA) receptor modulation via nutraceuticals that down-regulate the excitatory glutamate pathway or via calcium/sodium channel regulation, e.g., zinc or magnesium (8, 17); and antioxidant activity such as from N-acetyl cysteine (NAC) (18).

The adjunctive prescription of a specific nutraceutical with a mood stabilizer may have a

potential *synergistic* effect on one or more of the previously detailed pharmacodynamic activities, and this may in turn enhance the attenuation of a manic episode or enhance mood in bipolar depression. The concept of synergy relates to the idea that use of combinations of drugs (or nutraceuticals) may provide a *super additive* biological effect, as opposed to being just the sum of their individual parts (e.g.,  $1 + 1 = 5$ , not 2) (19). Epigenetic studies are already demonstrating that nutraceutical combinations can trigger the expression of additional genes beyond the effect of their isolated nutraceutical components (potentially by altered modification histone and DNA methylation) (20). Currently, there is an absence of preclinical studies exploring any potential additive or synergistic effects between nutraceuticals and pharmacotherapies, and this remains an area of research promise.

The aim of this review is to provide an analysis of the literature focusing specifically on the current clinical evidence and mechanisms of action of adjunctive use of nutrient-based nutraceuticals with commonly used pharmacotherapies for bipolar mania and depression. A supplementary aim is to provide a perspective on integrative clinical applications of select nutraceuticals with conventional pharmacotherapies used in BD and future directions of research. This paper advances research in the area of adjunctive pharmacotherapeutic approaches to treat BD, providing the first specialized systematic review in this area.

### Methods

PubMed, CINAHL, Web of Science, and Cochrane Library databases were systematically searched during mid 2010 for human clinical trials using the search terms: *bipolar disorder*, *bipolar depression*, *bipolar mania*, *mania*, *hypomania*, and *cyclothymia*, along with nutrient-based nutraceutical search terms such as *omega-3*, *vitamins*, *minerals*, and *amino acids*. A forward search of the identified papers was subsequently performed using Web of Science cited reference search, in addition to hand-searching the literature, contacting authors and academics for studies in the area, and searching the internet for grey literature. The literature was also searched for preclinical studies exploring the mechanisms of action of these nutraceuticals. Inclusion criteria consisted of human studies that were either open-label or controlled, involving nutraceuticals used adjunctively with existing medication or with treatment as usual for participants with diagnosed bipolar depression or mania. Studies included must have used measured

outcomes on established psychiatric scales and had a sample size > 10.

Effect sizes were calculated in all trials where data were statistically significant, and where data were not available, authors were contacted via email for the raw data (baseline and post-treatment scores and standard deviations). The effect size from clinical trial data was calculated as Cohen's *d* (21) by calculating the difference of baseline and post-treatment outcome scores between intervention and placebo and dividing this difference by the pooled baseline standard deviation. Where these data were not available, the effect size was calculated via conversion from *F*-scores and sample size. In the case where an effect size was already calculated [cf., Berk et al. (22)], we detailed this result.

## Results

### Overview

An initial search revealed 1,710 potential studies of interest, of which 18 met inclusion criteria (Fig. 1). Clinical trials were located using the terms: *omega-3*, *NAC*, *inositol*, *vitamin and mineral combinations*, *folic acid*, *magnesium*, and *branched-chain amino acids*. The mean trial length was 17 weeks (range: 1–52 weeks) with mean sample sizes of 39 participants (range: 12–121), and a mean age of 38 (Table 1). Of the 18 studies reviewed, 15 were randomized, double-blind, and placebo controlled, while the studies of Chiu et al. (23), Clayton et al. (24), and Osher et al. (25) were open-label. An adequate dosage and duration of treatment, as well as adequately reported data was available for most studies [Gracious et al. (26) subsequently sent raw data for analysis]. The Chiu et al. study (23) had methodological issues: (i) they did not report the mean age; (ii) they had a small sample size ( $n = 15$ ); (iii) they had a short duration of treatment (four weeks); and (iv) they had a low baseline depression level (mean baseline = 1.05) on the Hamilton Depression Rating Scale (HAMD) (27). Sample sizes, outcome measures, co-medications used, and duration of treatment were inconsistent between trials.

### Omega-3 fatty acids (Table 1)

Of the nine omega-3 studies, seven used a randomized, double-blind, placebo controlled design. Omega-3 interventions revealed positive (statistically significant) results on depression in four out of nine studies, with the two positive controlled studies (28, 29) having large effect sizes. In respect

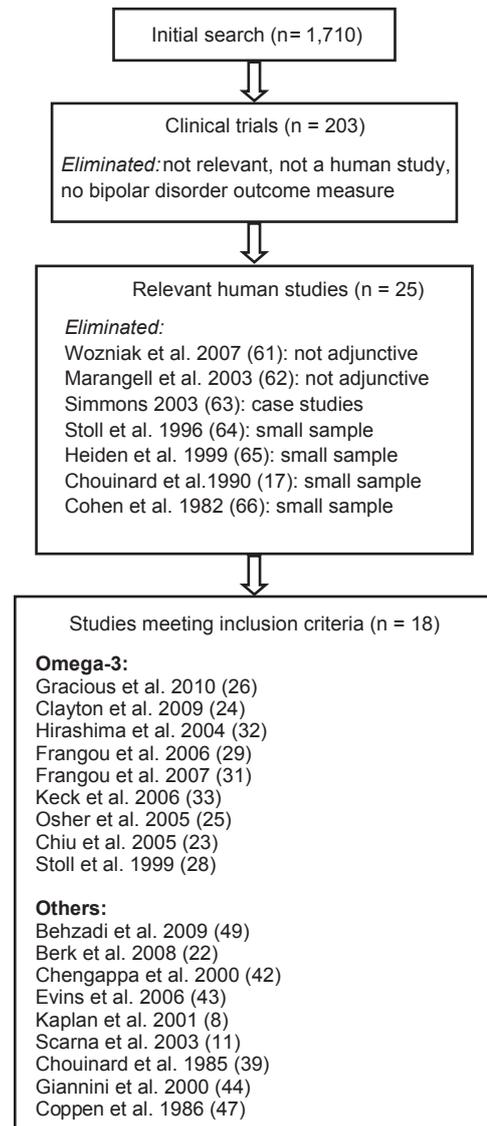


Fig. 1. Systematic review inclusion flow-chart.

to the effects on the outcome of mania, no omega-3 study revealed a positive finding in comparison to controls. All studies were, however, in favor of omega-3, and the small sample sizes may have reduced the chance of a significant effect. Heterogeneity was found between the nine studies in respect to the type of omega-3 preparation (high EPA/DHA blend, EPA, flaxseed oil, EPA/DHA 2:1 ratio), and dosage per day (DHA up to 3400 mg, ethyl-EPA 6000 mg,  $\alpha$ -LNA 6600 mg).

Of the two non-controlled studies located, a 26-week open-label adjunctive study by Osher and colleagues (25) in 12 participants with bipolar I disorder (BD-I) found that eight out of ten participants with one month of EPA were responders on the HAMD. Clayton et al. (24) conducted a six-week study involving 18 adolescents with BD-I or bipolar II disorder (BD-II) using omega-3

Table 1. Clinical trials using omega-3 for bipolar disorder (BD)

Intervention	Study	Dose	Design	Duration (weeks)	Patients (n)	Age (mean)	Sample	Co-medication	Primary outcomes	Results	Effect size (Cohen's <i>d</i> )
EPA/DHA	Chiu et al. 2005 (23)	EPA 4.4 g/day, DHA 2.4 g/day, or PLA capsules (olive oil)	Ran DB PC	4	15	NA	DSM-IV BD-I (acute mania)	Valproate (fixed dose 20 mg/kg/day)	YMRS HAMD CGI-BP	Significant reductions in both groups on YMRS from baseline but no difference between groups	YMRS: NS HAMD: NS CGI-BP: NS
DHA/EPA	Clayton et al. 2009 (24)	DHA 1560 mg, EPA 360 mg per day	Open	6	18	13	DSM-IV-TR BD-I, BD-II (juveniles)	Mood stabilizers (valproate, lithium, quetiapine)	YMRS HAMD C-GAS	Clinician rating of mania and depression was significantly lower from baseline	YMRS: 4.21 <sup>b</sup> HAMD: 4.10 <sup>b</sup>
EPA	Frangou et al. 2006 (29)	EPA 2 g/day or liquid paraffin PLA capsules	Ran DB PC	12	14	42	DSM-IV BD-I HAMD-17 > 10 (women)	Stable lithium	HAMD	No statistically significant differences were found between the groups on HAMD	HAMD: NS
EPA	Frangou et al. 2007 (31)	EPA 1 g or 2 g per day versus PLA capsules (liquid paraffin)	Ran DB PC	12	75	47	DSM-IV BD-I, BD-II HAMD-17 > 10	Stable psychotropic medication > 8 weeks	HAMD-17 YMRS CGI	A significant reduction of 1 g and 2 g EPA vs. PLA on HAMD and CGI	HAMD: (0.90 <sup>c</sup> , 0.50 <sup>d</sup> ) YMRS: NS CGI: (0.70 <sup>c</sup> , 0.70 <sup>d</sup> )
Flaxseed oil	Gracious et al. 2010 (26)	Flaxseed oil capsules titrated to maximum of 6.6 g $\alpha$ -LNA versus PLA capsules (olive oil)	Ran DB PC	16	51	13	DSM-IV BD-I, BD-II YMRS $\geq$ 4 (children and adolescents)	Stable psychotropic medication	CGI-BP YMRS CDRS-R	No significant differences between groups occurred. Less dropouts on flax oil than PLA	CGI-BP: NS YMRS: NS CDRS-R: NS

Table 1. (Continued)

Intervention	Study	Dose	Design	Duration (weeks)	Patients (n)	Age (mean)	Sample	Co-medication	Primary outcomes	Results	Effect size (Cohen's d)
EPA/DHA	Hirashima et al. 2004 (32)	EPA 5.0–5.2 g, DHA 3.0–3.4 g, or non-treatment control	PC	4	21	34	DSM-IV BD-I	Mood stabilizers (lithium, valproate, other anticonvulsants)	YMRS HAM-D-23	No significant differences between the omega-3 group and controls on mania or depression outcome	YMRS: NS HAM-D: NS
EPA	Keck et al. 2006 (33)	EPA 6 g/day or PLA capsules (liquid paraffin)	Ran DB PC	16	121	44	DSM-IV BD-I, BD-II, or BD-NOS (current MDD or rapid cycling)	A stable therapeutic dose of a mood stabilizer	YMRS IDS-C CGI-mania	No significant differences between EPA or PLA was found on any outcome	YMRS: NS IDS-C: NS CGI: NS
EPA	Osher et al. 2005 (25)	EPA 1.5 g to 2 g per day	Open	26	12	43	DSM-IV BD-I	Various psychotropics	HAM-D-24	8/10 participants with > 1 month of EPA had clinical response on HAM-D	HAMD: 1.23 <sup>b</sup>
EPA/DHA	Stoll et al. 1999 (28)	EPA 6.2 g/day, DHA 3.4 g/day vs. PLA capsules (olive ethyl esters)	Ran DB PC	16	44 <sup>a</sup>	43	DSM-IV screening for mania and depression	Medication treatment as usual	HAMD YMRS CGI GAS	Omega-3 group significantly reduced HAMD scores and increased CGI and GAS over PLA	HAMD: 1.40 YMRS: NS CGI: 1.52 GAS: 0.89

PLA = placebo; Ran = randomized; DB = double-blind; PC = placebo-controlled; Open = open-label; BD-I = bipolar I disorder; BD-II = bipolar II disorder; BD-NOS = bipolar disorder not otherwise specified; HAM-D = Hamilton Depression Rating Scale; YMRS = Young Mania Rating Scale; MDD = major depressive disorder; CGI = Clinical Global Impressions; CGI-BP = Clinical Global Impression–bipolar disorder; GAS = Global Assessment Scale; C-GAS = Children's Global Assessment Scale; CDRS-R = Children's Depression Rating Scale; IDS-C = Inventory of Depressive Symptomatology.

<sup>a</sup>30 completers with data available for analysis.

<sup>b</sup>Large effect sizes due to open-label design.

<sup>c</sup>1 g of EPA.

<sup>d</sup>2 g of EPA.

(DHA 1560 mg/day and EPA 360 mg/day) and found significantly reduced clinician-rated depression and mania scores from baseline. Of the controlled studies located, the first published random clinical trial (RCT) involving 44 participants using a combination of EPA and DHA (9.6 g/day) with conventional drug therapies revealed positive results with a large effect size on the HAMD (28). No significant effect on the Young Mania Rating Scale (YMRS) (30) mania outcome was found. A 12-week, three-arm controlled study involving 75 participants using 1 or 2 g of EPA combined with standard psychotropic medication revealed a small but significantly greater reduction on the HAMD (with a strong clinical effect) from either dose, compared with placebo (29). However, no significant effect for YMRS mania was achieved. A later controlled study conducted by the lead author (31) using 2 g of EPA versus placebo over 12 weeks in 14 female participants with BD-I revealed positive, but not statistically significant, effects on depression outcomes. A four-week adjunctive study by Hirashima et al. (32) involving 21 participants with BD-I revealed no significant differences between EPA (5 g) plus DHA (3 g) and a non-treatment control. However, an analysis of brain resonance imaging showed that T<sub>2</sub> levels were significantly reduced in the treatment group, denoting increased neuronal cell membrane fluidity. While a small RCT (n = 15) using 4.4 g of EPA/day and 6.6 g of DHA/day adjunctively with 20 mg/kg/day of valproate also found no benefit over placebo for reducing mania (23). A larger study involving 121 participants diagnosed with rapidly cycling BD using 6 g of EPA in combination with at least one mood stabilizer in patients, also found no benefit over placebo on reducing YMRS mania scores (33).

The mechanistic underpinnings of omega-3's activity that may assist in mood stabilization include inhibition of cell-signalling pathways via effects such as T<sub>2</sub> reduction (increasing cell membrane fluidity) (32), anti-inflammation via select cytokine (14, 34) and arachidonic acid inhibition (35), and PI-protein kinase-C antagonism (15). A potential thymoleptic effect beneficial in bipolar depression may occur via reuptake inhibition of serotonin and dopamine (in addition to modulation of secondary messengers, and enhanced cell membrane fluidity) (36).

Amino acids (see Table 2)

Of the other nutraceuticals, NAC, an amino acid with strong anti-oxidant properties, was found in

novel research by Berk and colleagues (22) to have a significant effect on improving depression levels in BD. The 24-week RCT used 1 g of NAC twice per day versus placebo in a sample of 75 participants stable on medication or therapy with DSM-IV-TR diagnosed BD-I or BD-II. Results revealed that NAC significantly reduced depression scored on the Montgomery-Åsberg Depression Rating Scale (MADRS) (37), with a large effect size. No significant effect was found on mania outcomes, although baseline YMRS mania levels were very low, suggesting a possible floor effect. NAC's effect may be due to neuroprotective antioxidant properties and from the sulfur protein supporting glutathione production (18).

In one study (11) using a blend of the branched amino acids leucine, isoleucine, and valine (60 g/day) versus placebo in 25 BD-I patients, a positive result was found with significant reductions in favor of the amino acid combination in reducing the severity of mania within six hours on the Beigel Manic State Rating Scale. The activity of these branched chain amino acids may be due to competitive inhibition of phenylalanine and tyrosine which are involved in dopamine production (11, 38). A two-week study using 12 g of the amino acid L-tryptophan in 24 participants with mania found potential benefits for reducing mania (39). The two-phase trial found that measures of mania were significantly reduced with L-tryptophan on Clinical Global Inventory (for mania), with a large effect size, in the initial open-phase and continued but lessened during the controlled-phase. Restricting or excluding L-tryptophan from the diet may increase the susceptibility of BD patients to depressive mood swings, though research findings to date are highly inconsistent (40). The beneficial effect of L-tryptophan in reducing depression scores in people with unipolar depression has been demonstrated in a number of clinical studies, but the quality of these studies is generally poor [for review, see (7)]. The potential hypnotic action of the amino acid via serotonergic mechanisms may be of potential benefit in sleep regulation (41).

Vitamins and minerals (see Table 2)

In the literature search, two studies were located using the glucose isomer inositol. An initial six-week controlled study by Chengappa et al. (42) using 12 g of inositol in 24 participants primarily with BD-I found a significant reduction of MADRS depression scores after three weeks of treatment. This significance was, however, not maintained by Week 6 at the conclusion of the study. A later six-week augmentation study using

Table 2. Clinical trials using nutrients in bipolar disorder (BD)

Intervention	Study	Dose	Design	Duration (weeks)	Patients (n)	Age (mean)	Sample	Co-medication	Primary outcomes	Results	Effect size (Cohen's <i>d</i> )
N-acetyl cysteine (NAC)	Berk et al. 2008 (22)	1 g NAC twice/day vs. PLA tablets (PNS)	Ran DB PC	24	75	46	DSM-IV BD-I, BD-II	Stabilized medication or therapy	MADRS BDRS YMRS	NAC significantly reduced depression on MADRS and BDRS after Week 20.	MADRS: 1.04 BDRS: 0.83 YMRS: NS
Inositol	Chengappa et al. 2000 (42)	12 g inositol vs. PLA tablets (D-glucose)	Ran DB PC	6	24	43	DSM-IV BD-I, BD-II HAMD >15	Stable doses of lithium, valproate, or carbamazepine	HAMD MADRS CGI	No effect on YMRS 8/12 of inositol group completers had clinical response on MADRS. No significant effect between groups	HAMD: NS MADRS: NS
Inositol	Evins et al. 2006 (43)	2.5–10.0 g inositol twice/day vs. PLA (lactose tablets)	Ran DB PC	6	17	45	DSM-IV BD-I, BD-II HAMD >15	Stabilized (> 2 wks) therapeutic levels of lithium or valproate	HAMD YMRS	Clinical response in 4/9 inositol vs. 0/8 PLA. No significant differences between groups on HAMD or YMRS	HAMD: NS YMRS: NS
36-ingredient nutraceutical (vitamins and minerals)	Kaplan et al. 2001 (8)	High dose nutraceutical 8 capsules 4 times/day	Open	3 + 36 (average)	14	29	DSM-IV BD-I, BD-II, or BD-NOS	Stabilized (> 4 wks) medication	HAMD BDRS YMRS	Clinical response in 55% of completers (6/11). Large and significant reduction on all outcomes	HAMD: 1.70 BDRS: 0.89 YMRS: 0.83
Branch-chain amino acids [(BCAA): isoleucine, leucine, valine]	Scarna et al. 2003 (11)	60 g BCAA/day (a.m.) vs. inert control drink	Ran DB PC	1	25	41	DSM-IV BD-I with current mania	Any psychotropic except sodium valproate	BMSRS	BCAA significantly reduced mania over PLA over 6 hrs and persisted after 7 days <sup>b</sup>	BMSRS: 1.60
L-tryptophan	Chouinard et al. 1985 (39)	12 g tryptophan 4 times/day vs. PLA tablets (PNS)	Open (first phase) <sup>a</sup> Ran DB PC	2	24	44	DSM-III mania	Initial haloperidol as required	CGI-man mania	Open phase: CGI-man total reduced significantly. Controlled phase: a trend occurred in favor of tryptophan over PLA	CGI-total: 1.47
Magnesium	Giannini et al. 2000 (44)	375 mg magnesium oxide/day vs. glucose PLA	Ran DB PC	16	20	26	Prior DSM-IV diagnosed mania (>6 months)	Stable verapamil (>6 months)	BPRS	Magnesium group had a significant reduction of mania levels on BPRS compared to PLA at Week 16	BPRS: 1.44

Table 2. (Continued)

Intervention	Study	Dose	Design	Duration (weeks)	Patients (n)	Age (mean)	Sample	Co-medication	Primary outcomes	Results	Effect size (Cohen's <i>d</i> )
Folic acid	Coppen et al. 1986 (47)	200 IU folic acid vs. PLA tablets (PNS)	Ran DB PC	52	17	58	Patients currently taking lithium (diagnosis not specified)	Stable lithium (>12 months)	BDI AMI	A subsample of 17 BD patients completed 52 wks of treatment. No significant differences were found between groups	BDI: NS AMI: NS
Folic acid	Behzadi et al. 2009 (49)	3 mg of folic acid or matching PLA	Ran DB PC	3	88	35	BD-I with current acute mania	Initiated sodium valproate	YMRS	Significant differences between groups were found after 3 wks of treatment. Notably, no effect was found in the first 2 wks	YMRS: 0.40

PLA = placebo; PNS = placebo not specified; Ran = randomized; DB = double-blind; PC = placebo-controlled; Open = open-label; BD-I = bipolar I disorder; BD-II = bipolar II disorder; BD-NOS = bipolar disorder not otherwise specified; HAMD = Hamilton Depression Rating Scale; MADRS = Montgomery-Åsberg Depression Rating Scale; BDRS = Bipolar Depression Rating Scale; YMRS = Young Mania Rating Scale; CGI = Clinical Global Impressions; BMSRS = Beigel Manic State Rating Scale; BPRS = Brief Psychiatric Rating Scale; BDI = Beck Depression Inventory; AMI = Affective Morbidity Index; clinical response = ≥ 50% reduction on assessment scale.

<sup>a</sup>Open study for first week then randomized in second week.

<sup>b</sup>Completer analysis.

5–20 g of inositol in 17 participants with BD-I or BD-II on stable pharmacotherapies also found no significant reduction on depression or mania outcomes (43). The two inositol studies (42, 43) did, however, find greater clinical response by the nutraceutical over control, and in the Chengappa et al. study (42), five of the six responders in the open-extension continuation maintained response. Small sample sizes may have prevented a significant result on intergroup analysis, thus stable inositol levels are posited as being a potentially beneficial effect in BD (43).

The effect of magnesium as an adjunctive therapy for the treatment of acute mania or rapidly cycling BD has been examined in one small RCT (44). This RCT used 375 mg of magnesium oxide versus glucose placebo over 16 weeks in 20 male participants with prior DSM-IV diagnosed mania and >6 months on a mood stabilizer (verapamil). Results revealed a significant reduction in mania with a large effect size compared to controls at Week 16. Magnesium has been shown in animal models to have anti-anxiety properties (45), and may potentially enhance mood stabilization via modulating calcium channel activity to improve membrane stability and assist in regulating neurotransmitter release (46). Furthermore, verapamil and magnesium share similar calcium-regulatory action, and may modulate adrenergic activity, suggesting an additive or synergistic effect may be possible with these two treatments.

A small open study using a multi-component nutrient formula on 14 participants with various BD diagnoses revealed positive clinical responses in 55% of completers, with large effect sizes on depression and mania outcomes (8). It has been postulated by Kaplan and colleagues (8) that multi-nutrient formulations may assist in cases of nutritional deficiency, assist in correcting *metabolic errors*, and may modulate enzymatic and secondary messenger function (necessary for proper neurochemical transmission).

In a study by Coppen and colleagues (47) using folic acid on a subsample of BD participants (n = 17), no statistically significant differences occurred on symptoms of depression between groups after 52 weeks. However, low baseline depression levels [1.6 on the Beck Depression Inventory (48)] restrict the likelihood of an effect. A recent study by Behzadi et al. (49) involving 88 participants with acute mania who were initiated on valproate, showed a significant reduction of mania on the YMRS (medium effect size) after three weeks of high-dose folic acid (3 g) compared to placebo. This effect was not evident during the first two weeks. Folic acid may have an effect on

BD by modulating the ‘one-carbon cycle’ which along with B6 and B12 regulates homocysteine and S-adenosyl methionine production (50).

## Discussion

This current review is the first specific systematic review of adjunctive nutraceutical studies in the treatment of bipolar depression and mania. The review included a rigorous literature search process and methodological analysis. Overall, results revealed positive effects for various nutraceuticals to improve outcomes on bipolar depression and mania. In summary, regarding nutrients for treating bipolar depression, positive evidence were found for NAC and a chelated mineral and vitamin formula. On the outcome of bipolar mania, several nutraceuticals significantly ameliorated bipolar mania: a chelated mineral formula, L-tryptophan, magnesium, folic acid, and branched-chain amino acids. Conclusions, however, from the positive results with large effect sizes should be tempered, as many trials involved small sample sizes and have not yet been replicated in larger clinical trials. Furthermore, two confounding factors should be considered. First, the reviewed studies did not explore participants’ dietary patterns (this may influence potential response to nutrient supplementation). Second, different nutritional therapies may have differential effects in either the depression or mania phases of BD. Therefore, it is challenging to examine the effect of a treatment on either depression or mania when participants may cycle between these mood states during the course of a study. A limitation specific to this review is that a meta-analysis could not be conducted as the varied types of nutraceuticals covered in this review provide too much heterogeneity and with omega-3, an abundance of meta-analyses already exist examining effects on mood. For a recent meta-analysis on omega-3 and mood disorders consult Appleton et al. (51).

In respect to omega-3, while mixed results occurred on bipolar depression, all results were in favor of the nutraceutical, and small sample sizes in many instances may have led to insignificant results. Consistent results showed no significant effect on mania. Preparation and dosage were, however, markedly different across the studies, with isolated and purified DHA and/or EPA, and fish oil or flax oil being employed. Although it appears that EPA (or higher EPA to DHA ratio) preparations have a potentially stronger antidepressant effect, as revealed in a recent review by Martins (52). The meta-analytic comparison between DHA and EPA found that DHA

monotherapy was not significant, whereas in studies using supplements containing greater than 50% EPA, a significant effect occurred in favor of omega-3 [standardized mean difference =  $-0.446$ ; 95% confidence interval (CI):  $-0.753$  to  $-0.138$ ;  $z = -2.843$ ;  $p = 0.005$ ]. Omega-3 use in cases of deficiency or comorbid cardiovascular disease may still be warranted, especially for persons on psychotropic medications that increase weight gain and cause metabolic disturbance (53).

A total of 10 out of 18 studies provided details of adverse reactions and safety issues. In several studies (8, 23, 26, 28, 29, 42), no significant adverse reactions were found in the intervention group. Nausea and digestive disturbance was found to significantly occur in studies using a branched-chain amino acid formulation (11), L-tryptophan (39), EPA (33), and EPA/DHA (24). Although the studies used small samples and various types of nutraceuticals no major adverse reactions were found to occur, thus this therapeutic strategy appears to not present with any obvious safety concerns beyond that of normal prescriptive considerations with conventional pharmacotherapies.

While further research is required to replicate the results of many of the studies reviewed to allow for firm conclusions to be reached, current evidence of select nutraceuticals may cautiously encourage clinicians to consider various nutrient adjunctive options for treating BD. Caveats to prescription include the use of quality nutrient products and correct doses. While expense may be an issue, the general cost of the nutraceuticals reviewed appears to be modest compared to newer generation pharmacotherapies. While the potential for decreased side effects by reducing the dose of medication (within therapeutic range) may be appealing, as Popper (10) cautions, introducing nutraceuticals at higher doses too quickly into the system may potentially cause adverse effects; thus increasing the dose gradually may be advised.

Challenges should be noted regarding research in the area of studying nutraceuticals in BD. While this review focused on the DSM-IV classification of BD, nutraceuticals have multiple effects that are not necessarily constrained by a diagnostic category. While it is accepted within the current medical paradigm to confine research to diagnosed areas, other studies not reviewed in this paper provide evidence of nutraceuticals having a range of effects on mental health domains e.g., sleep, mood, and anxiety (7). Another over-arching difficulty in studying a BD population is the natural rhythmicity between mania and depressive phases. It may be potentially found that certain nutraceuticals, such as magnesium, are better

served in the manic phase, while others such as NAC are more effective in the depressive phase. This warrants more attention.

In respect to dietary habit, which may be a confounding factor in the potential benefit of nutraceutical prescription, cross-sectional studies have demonstrated that people with BD have poorer diets than healthy controls. Kilbourne et al. (54) revealed that a random sample of 2,032 people with BD, compared to a control cohort, had significantly poorer dietary habits and fewer servings of fruits and vegetables. A recent exploratory analysis by Jacka and colleagues (55) of the dietary patterns of a small sample ( $n = 23$ ) of women with BD, found that compared with the *no psychopathology* control cohort ( $n = 691$ ), that a Western or modern dietary pattern (higher in refined sugars, processed foods, and fats) was significantly associated with increased risk of BD. Western diets have been associated with higher levels of C-reactive protein (56) and lower brain-derived neurotropic factor (57), while traditional Mediterranean diets (higher in vegetables, fruits, legumes, whole grains, and olive oil) are associated with lower inflammatory cytokines (58) and are less correlated with depression (59). Nutritional deficiencies may arise from poor dietary patterns and thus nutraceutical interventions may, in part, address this. However, it is currently unknown whether this application may exert an effect via addressing a correction of an underlying nutritional deficiency or via a specific pharmacodynamic effect.

Future research into the field of augmentation appears to be warranted based on various preliminary positive findings discussed in our review. The direction of research into omega-3 should involve the use of a mixed EPA/DHA blend, with a higher ratio of EPA to DHA, in a large sample of BD subjects over a period of one year to definitively assess whether the intervention is effective in manic and depressive episodes. In addition, future studies should also assess any effect on increasing remission via long-term omega-3 supplementation and early intervention in subthreshold BD symptoms [such as was effective in Amminger et al. (60)]. Overall, many of the reviewed-studies sample sizes were too small and thus inconclusive results may be due to statistical under-powering. Replicated studies using large samples should occur with NAC, magnesium, folic acid, and various amino acids.

In summary, although the evidence does not currently support adjunctive use of omega-3 for bipolar mania, it may have a potential use in bipolar depression. While several other select nutraceuticals in conjunction with conventional pharmacotherapies are developing an emerging

evidence base, there is currently not sufficient evidence to support mainstream clinical application.

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