JOURNAL OF CHILD AND ADOLESCENT PSYCHOPHARMACOLOGY
Volume 23, Number 8, 2013

Pp. 558–567
DOI: 10.1089/cap.2012.0098

Nutritional and Safety Outcomes from an Open-Label Micronutrient Intervention for Pediatric Bipolar Spectrum Disorders

Elisabeth A. Frazier, PhD, Barbara Gracious, PhD, L. Eugene Arnold, MD, MEd, Mark Failla, PhD, Chureeporn Chitchumroonchokchai, PhD, Diane Habash, PhD, RD, LD, and Mary A. Fristad, PhD, ABPP

Abstract

Objective: The purpose of this study was to report the safety, tolerability, and serum micronutrient concentrations and their correlations with mood changes from an 8 week pilot feasibility study of a 36 ingredient multinutrient supplement, EM-Powerplus (EMP+), for pediatric bipolar spectrum disorders (BPSD).

Methods: Ten children ages 6–12 received EMP+ escalating from one to four capsules t.i.d., with four children increased to the maximum suggested dose, five capsules t.i.d. Outcome measures were micronutrient concentrations in serum and red blood cells, vital signs, body mass index (BMI), dietary intake (Food Frequency Questionnaire and 24 hour dietary recall interview), and mood and global functioning ratings.

Results: Seven children (70%) completed the study. Three (30%) terminated early for tolerability and compliance issues. Adverse effects were mild and transient, and chiefly consisted of initial insomnia or gastrointestinal (GI) upset. No differences occurred in BMI ($p = 0.310$) or waist–hip ratio (WHR; $p = 0.674$) pre- to postsupplementation. Four of the tested serum vitamin concentrations increased from pre- to postsupplementation: vitamin A-retinol, vitamin B6, vitamin E-α-tocopherol; and folate (all $p < 0.05$). The increase in serum 25-OH vitamin D approached significance ($p = 0.063$). No differences were found in dietary intake pre- to postsupplementation, suggesting that blood nutrient level increases were caused by EMP+.

Conclusions: In this open prospective study, short-term use of EMP+ in children with BPSD appeared safe and well-tolerated, with a side effect profile preferable to first-line psychotropic drugs for pediatric bipolar spectrum disorders. A double-blind, randomized clinical trial is feasible, appears safe, and is warranted by open-label clinical outcomes and plausible mechanisms of action, combined with documentation of increased serum concentrations of specific micronutrients.

Introduction

Treatment research for childhood bipolar spectrum disorders (BPSD) is limited. Clinical care guidelines rely on psychotropic medications shown to be helpful as first-line treatment for bipolar I disorder (BP-I), including second-generation antipsychotics and the classic mood stabilizers lithium and divalproex sodium. Unfortunately, all are associated with significant adverse effects (Kowatch et al. 2005, 2009). A medical claim study found higher rates of a variety of adverse cardiometabolic effects in >4000 youth who had been prescribed an atypical antipsychotic or one of two conventional antipsychotics, than in a random sample of 4500 youth not treated with psychotropics (McIntyre and Jerrell 2008). An open-label study of second-generation antipsychotic treatment in inpatient youth with various psychiatric diagnoses showed weight gain with all (including aripiprazole, olanzapine, quetiapine, and risperidone), after 12 weeks, compared with youth who had received no treatment. Increases were also seen for serum triglycerides, total cholesterol, non-high-density lipoprotein (non-HDL) cholesterol, and triglyceride:HDL-cholesterol ratios with olanzapine and quetiapine, and higher triglyceride concentrations with risperidone (Correll et al. 2009). In addition to obesity and risk for hypertension and type 2 diabetes mellitus, potential deleterious effects of second-generation antipsychotics also include drowsiness, lethargy, orthostatic hypotension, nasal congestion, rigidity, tremor, and dystonia (Fleischhaker et al. 2006). Novel treatments that are effective and free of such adverse effects are greatly needed.

Micronutrient supplementation may have beneficial effects on mood disorders, but the study of therapeutic use for such is in its infancy. Many vitamins and minerals are essential for neurological development and integrity as factors required for synthesis of neurotransmitters, cognition, and protection against oxidative stress (Shils et al. 2006). Nutrients are fundamental to physical and

Department of Psychiatry, Department of Human Nutrition, The Ohio State University, Columbus, Ohio.
Funding: This study was funded by a grant from the Psychiatric Research Foundation, a local private foundation.

mental health, and may possibly be useful in reducing symptoms of BPSD without the side effects of contemporary pharmaceuticals. Multi-ingredient supplements in particular require scientific study both because of their increasing use in children for a variety of disorders without supportive evidence, and because of theoretical claims that nutrients do not work independently in the human body, but rather depend upon balanced ratios among multiple nutrients for optimal function. That is, a deficiency of one nutrient may affect the adequacy of others (Kaplan et al. 2007; Benton 2008).

One micronutrient supplement that appears to have potential benefit in a variety of mental disorders is EMPowerplus (EMP+; Truehope Nutritional Support Ltd., Raymond, Alberta, Canada; www.truehope.com). The 36 ingredient supplement consists of 16 minerals, 14 vitamins, 3 amino acids and 3 antioxidants (formulation, Table 1). In 2008 alone, >2000 children were administered this supplement for mood concerns (Truehope, personal communication, May 7, 2008), but randomized controlled trials (RCTs) have not been conducted in children with mood disorders. Results from an animal study (Halliwell and Kolb 2003), case studies, and open-label trials in both youth and adults support benefit for mood symptoms (Kaplan et al. 2001; Popper 2001; Kaplan et al. 2002; Simmons 2003; Kaplan et al., 2004; Frazier et al. 2009; Rucklidge 2009; Mehl-Madrona et al. 2010; Rucklidge and Harrison 2010; Rucklidge et al. 2010), self-injurious behavior (Mehl-Madrona et al. 2010), hyperactivity/impulsivity (Mehl-Madrona et al. 2010; Rucklidge & Harrison 2010; Rucklidge et al. 2010), inattention (Rucklidge et al. 2010), and anxiety (Kaplan et al. 2002; Frazier et al. 2009; Rucklidge 2009; Rucklidge and Harrison 2010; Rucklidge et al. 2010). These results call for additional scientific investigation.

To date, safety and tolerability data on the 36 ingredient formula comprising the EMP+ supplement suggest no toxicities or clinically meaningful negative outcomes based on biological safety data from 144 youth and adults who have taken EMP+ in the context of a research study (Simpson et al. 2011). Of the available adverse event information gleaned from six research studies of 157 youth and adults, participant reports of adverse events consisted of minor, transient nausea and/or headache (Simpson et al. 2011). In a naturalistic case–control study of EMP+ versus contemporary medication in children with autism, fewer adverse events were reported in the EMP+ group (33) compared with the medication group (214), and none of the 22 types of adverse events were reported more frequently in the EMP+ than in the medication group (Mehl-Madrona et al. 2010).

We previously reported that 10 children treated with EMP+ demonstrated a mean 37% decrease in depression scores ($p < 0.06$)

Table 1. Composition of 36 Ingredient EMPowerPlus Supplement

Ingredient	*1 capsule*	*4 capsules*	*8 capsules*	*15 capsules*	*unit*
Vitamin A (retinyl palmitate)	384	1536	3072	5760	IU
Vitamin C (ascorbic acid)	40	160	320	600	mg
Vitamin D (cholecalciferol)	96	384	768	1440	IU
Vitamin E (d-α-tocopheryl succinate)	24	96	192	360	IU
Vitamin B1 (thiamine mononitrate)	1.2	4.8	9.6	18	mg
Vitamin B2 (riboflavin)	0.9	3.6	7.2	13.5	mg
Vitamin B3 (niacinamide)	6	24	48	90	mg
Vitamin B5 (pantothenic acid as d-calcium pantothenate)	1.4	5.8	11.5	21.6	mg
Vitamin B6 (pyridoxine hydrochloride)	2.4	9.6	19.2	36	mg
Vitamin B9 (folic acid)	96	384	768	1440	μg
Vitamin B12 (cyanocobalamin)	60	240	480	900	μg
Vitamin H (biotin)	72	288	576	1080	μg
Choline bitartrate	36	144	288	540	mg
Inositol	12	48	96	180	mg
Calcium (chelate)	88	352	704	1320	mg
Iron (chelate)	0.9	3.7	7.3	13.74	mg
Phosphorus (chelate)	56	224	448	840	mg
Iodine (from Pacific kelp)	13.6	54.4	108.8	204	μg
Magnesium (chelate)	40	160	320	600	mg
Zinc (chelate)	3.2	12.8	25.6	48	mg
Selenium (chelate)	13.6	54.4	108.8	204	μg
Copper (chelate)	0.5	1.9	3.8	7.2	mg
Manganese (chelate)	0.6	2.6	5.1	9.6	mg
Chromium (chelate)	41.6	166.4	332.8	624	μg
Molybdenum (chelate)	9.6	38.4	76.8	144	μg
Potassium (chelate)	16	64	128	240	mg
Germanium sesquioxide	1.4	5.5	11	20.7	mg
Boron (chelate)	160	640	1280	2400	μg
Nickel (chelate)	2	7.8	15.7	29.4	μg
Vanadium (chelate)	79.6	318.4	636.8	1194	μg
dl-phenylalanine	24	96	192	360	mg
L-glutamine	12	48	96	180	mg
L-methionine	4	16	32	60	mg
Citrus bioflavonoids	16	64	128	240	mg
Grape seed	3	12	24	45	mg
Ginkgo biloba(leaf)	2.4	9.6	19.2	36	mg

and a 45% decrease in mania scores ($p < 0.01$; Frazier et al. 2012). Among the seven children completing the study, there was a 71% decrease in depression scores ($p < 0.05$) and a 58% reduction in mania scores ($p < 0.05$). Here, we report the following features related to EMP+ treatment and response: 1) Safety measures, including physical parameters; 2) pre-post supplementation micronutrient blood level changes and any related associations with mood symptoms; and 3) dietary measures to determine whether changes associated with supplementation are related to dietary alterations. We hypothesized that supplementation with EMP+ for 8 weeks would be associated with no notable side effects, or changes in participants' nutritional intakes, body mass index (BMI), and waist–hip ratio (WHR). Moreover, we expected increases from baseline in serum concentrations of iron, magnesium, and zinc, as well as vitamins A, B6, D, E, and folate. We also conducted exploratory analyses to examine how changes in nutrient serum concentrations were related to changes in mood and global functioning.

Methods

Prior to study initiation, an Investigational New Drug (IND) approval was obtained from the Food and Drug Administration (FDA; IND#102,467) and the study was approved by the institutional review board of The Ohio State University. A parent/legal representative of each study patient provided written informed consent, and patients provided written assent prior to administration of any study procedures. Participation dates were from September 2008 to May 2009. Visits took place within the Harding Hospital, Department of Psychiatry at the Wexner Medical Center of The Ohio State University, and The Ohio State University Clinical Research Center.

Participants

Participants were required to swallow multiple capsules (training in swallowing was offered), and to tolerate being without psychotropic medication(s) for a minimum of 11 weeks (3 week washout + 8 week trial) to maintain ongoing eligibility. Exclusion criteria included intelligence quotient (IQ) <70, major medical disorders (e.g., diabetes, epilepsy, metabolic disorders), autism, psychotic symptoms, or active suicidal plan or intent. Participants were allowed to continue any ongoing psychosocial interventions, but they were not allowed to receive psychotropic intervention throughout the trial. Eleven children ages 6–12 years old completed screening procedures, and 10 were enrolled and participated in up to seven assessment visits with each parent–child pair over 8 weeks. Participants were a mean of 8.9 years at study entry (SD = 2.02) and 6/10 were male. Nine children were white-non Hispanic (90%) and one was white/Hispanic (10%). Global functioning, measured by the *Children's Global Assessment Scale* (CGAS: Shaffer et al. 1983) ranged from 41 to 55 (mean = 48.50, SD = 5.02). Mood diagnoses included: BP-I (10%); BP-not otherwise specified (NOS) (30%); and subthreshold BP-NOS (60%, of whom two met American Psychiatric Association: *Diagnostic and Statistical Manual of Mental Disorders*, 4th ed., Text Revision [DSM-IV-TR] [American Psychiatric Association 2000] diagnostic criteria for major depressive disorder and one met diagnostic criteria for dysthymic disorder). (Please see Frazier and colleagues (2012) for an operationalized definition of subthreshold BP-NOS.) Comorbid Axis I disorders were present in all with nine having attention-deficit/hyperactivity disorder (ADHD), five having oppositional defiant disorder, four having conduct disorder, and six diagnosed with one or more comorbid anxiety disorders. Three children were taking psychotropic medications at the time of enrollment. They were tapered off these medications under supervision of their prescribing physician, and then completed the minimum 3 week washout period free of medication prior to beginning EMP+. More detailed information regarding pretrial medications can be found in the previously published Frazier and colleagues (2012) main outcomes article.

Dosing and adverse effects monitoring

Bottles of EMP+ provided by the manufacturer were given to the parents/guardians, who were instructed on dosing based on manufacturer recommendations. Dosage schedule was one capsule by mouth three times a day (t.i.d.), which increased by one capsule t.i.d. every 2 days up to four capsules t.i.d. (target dose). Participants were advised to take the capsules with food to reduce potential for gastrointestinal upset. Adverse effects were systematically recorded at each weekly visit with parent and child, and if these were none or minimal, and mood symptoms were still present per consensus between parent, rater, and principal investigators (PIs), dosage could be increased to five capsules t.i.d. at any time prior to end of study. Dosing could be reduced or titration slowed at any time for side effects, on permission from the PIs. Dosing remained unchanged when desirable treatment response was achieved. Participant adherence was checked by standard capsule counts of returned unused supplement capsules at each visit; compliance was encouraged by structured behavioral strategies, such as using in-school administration for noontime doses, as appropriate.

Measures

History, physical, and adverse effect measures. An initial comprehensive psychiatric and medical history including past and current medications was conducted by the study coordinator (EF). Physical examinations were performed at baseline and end of study by a certified pediatric nurse practitioner. Vital signs and height, weight, and waist and hip circumferences were obtained at each visit, using a standardized technique previously established by Clinical Research Center nurses. BMI and WHR were calculated. Adverse effects were obtained from parent and child via questioning using a semistructured side effect form designed by the PI to incorporate both previously reported adverse effects from EMP+, as well as those typical to antipsychotics. Participants were asked to rate the child's experience of 29 potential side effects commonly found in medical trials as ''absent, mild, moderate, or severe'' in addition to documenting any changes in sleep or eating habits. The study team also observed participants for alertness because of the potential for sedation related to magnesium supplementation.

Psychometric ratings measures. Measures of mood symptoms, global functioning, and symptom severity and improvement were collected at each visit using the Kiddie Schedule for Affective Disorders and Schizophrenia for School-Age Children-Present Episode (K-SADS)-Depression Rating Scale (KDRS; Chambers et al. 1985; Ambrosini et al. 1989), K-SADS-Mania Rating Scale (KMRS; Axelson et al. 2003), CGAS, and the Clinical Global Impressions Severity and Improvement Scales (CGI-S, CGI-I: National Institute of Mental Health 1985), respectively.

Dietary measures. Diet was monitored pre- and post-supplementation (baseline and week 8) using the standardized

United States Department of Agriculture (USDA) Automated Multiple Pass Method 24 hour recall (24hr; Conway et al. 2003) and a validated Food Frequency Questionnaire (FFQ), administered by a research dietitian (DH). FFQs were completed by parents to determine the child's dietary intake on an average week. The 24hr was completed with the child and parent to determine everything the participant had consumed the day prior to each blood draw (Weber et al. 2004; Wilson and Lewis 2004) and supplemented with plastic and paper food models to increase precision. Dietary records were kept via a standard log to account for vitamin and mineral intake from daily foods in addition to the supplement. Dietary records were entered into the Nutrition Data System for Research (NDS-R) software (Nutrition Data System for Research 2005a,b), a nutrient analysis program maintained by the Nutrition Coordinating Center (NCC) at the University of Minnesota School of Public Health.

Blood draws and micronutrient and inflammatory measures. A total of 39 mL of whole blood was drawn using sterile and universal precautions at baseline (week 0, visit 2) and end of study (week 8, visit 7). Levels of micronutrients supported in the literature as having beneficial central nervous system (CNS) or antioxidant effects chosen for assessment included iron, magnesium, zinc, and vitamins A, B6, D, E, and folate.

Laboratory analysis

Iron status was determined in two ways: 1) Grossly, from complete blood count hematological parameters; and 2) from assay of serum transferrin receptor (sTfR) and ferritin by enzyme-linked immunoassay (ELISA; Ramco Laboratories, Inc.). sTfR is a sensitive indicator of whole body iron status not subject to conditions that can affect classic biochemical indices such as serum iron, transferrin saturation, and ferritin (Cook et al. 1993; World Health Organization 2001). The sTfR/ferritin ratio is particularly useful for determining iron deficiency in the absence of anemia in children (Vazquez-Lopez et al. 2006). As ferritin levels are easily influenced by environmental factors in the body such as inflammation (Maes et al. 1996) and the menstrual cycle, sTfR is considered the more valid estimate of iron stores in the body. Magnesium level was measured via inductive coupled plasma-mass spectrometry (ICP-MS; Shaole et al. 1997). Plasma zinc was measured by atomic absorption spectrophotometry. Plasma pyridoxal-5-phosphate (PLP), the active isomer of vitamin B6, was determined using a radioassay kit (Buhlmann Laboratories AG, Switzerland). Vitamin A, 25-OH vitamin D, and plasma α- and γ-tocopherols (TC; vitamin E) were quantified by high-performance liquid chromatography (HPLC) with a photodiode detector using a method requiring only 0.10 mL plasma (Podda et al. 1996). Area under the curve (AUC) for analytes was compared with those of known quantities of pure standards using five point standard curves. Because of limitation of amount of samples, duplicated analysis of biological markers (both by ELISA and atomic absorption spectrometry [AAS]) were performed with the difference of two values from duplicated analysis acceptable at $<10\%$.

Statistical analyses

Safety. A series of related-samples Wilcoxon signed rank tests were calculated to examine changes in BMI and WHR between pre- and postsupplementation (baseline and week 8). These analyses included the seven participants who completed the entire study. Reported adverse effects were tallied for total incidents of each complaint as well as severity of each complaint (see Table 2).

Table 2. Frequency and Severity of Side Effects Reported Throughout the 8 Week Trial

Side effect	*Severity*	*No. of participants*
Initial insomnia	mild	3
Shakiness		0
Tongue movements		0
Muscles stiff or ''stuck''		0
Eyes ''stuck''		0
Headache		0
Dizziness		0
Constipation		0
Diarrhea		0
Dyspepsia		0
Nausea	mild	4
Vomiting	mild	1
Anxiety		0
Excessive saliva		0
Excessive appetite		0
Dry mouth		0
Blurred vision		0
Nocturnal enuresis	mild	1
Rhinitis		0
Menstrual problems		0
Coughing		0
Tachycardia		0
Seizures		0
Skin rash		0
Tinnitus		0
Weight gain		0

One instance of initial insomnia was believed to be related to the spring transition to Daylight Savings Time per parent report. The report of vomiting occurred when taking the supplement without food and resolved when taking the supplement on a full stomach. Per parent report, the incident of nocturnal enuresis was believed to be unrelated to supplementation.

Blood assays. A series of 10 nonparametric, one tailed Fisher's randomization tests were performed to analyze levels of various nutrients pre- and postsupplementation (baseline and week 8) on the seven participants who completed the entire study. Data were graphed to illustrate nutrient response to treatment. In an exploratory analysis, nonparametric Spearman's ρ correlations were calculated to examine the relationship between change in nutrient blood levels and change in mood and global functioning from pre- to postsupplementation.

Nutritional outcomes. A series of related-samples Wilcoxon signed rank tests were calculated to examine changes in dietary intake pre- to postsupplementation (baseline and week 8) with the seven participants completing the study.

Results

Dosing, duration of treatment, and concomitant medications

Seven children (70%) completed the study. Three participants (30%) terminated early because of difficulty swallowing the capsules despite training. Participants remained on supplementation for an average of 46.4 days (SD = 23.29, median = 55). Of the seven study completers, five completed the full 56 days of dosing and two only completed 54 days of dosing, as a result of scheduling. Excluding the two participants who had dropped out of the study prior

Table 3. Mean and Standard Deviation of Anthropometric Measures Pre- and Post-EMP+ Supplementation

	Pre-supplementation Mean (SD)	*Post-supplementation Mean (SD)*	p
Height (cm)	141.07 (18.78)	142.79 (18.88)	0.02
Weight (kg)	40.18 (19.66)	43.03 (23.26)	0.05
BMI	19.1 (3.91)	19.7 (5.11)	0.31
WHR (cm)	0.81 (0.05)	0.81 (0.07)	0.67

EMP+, EMPowerPlus; BMI, body mass index; WHR, waist-hip ratio.

to reaching a full dose, four children took 12 capsules a day and four took the maximum 15 capsules a day. Although asked not to change concomitant treatment during the study, one participant began taking dexmethylphenidate 10 mg per day between study visits 5 and 6, and continued through the remainder of the study, because of inattention and impulsivity impairing his school functioning. The addition of dexmethylphenidate (10 mg per day compared with 25 mg per day taken prior to washout) was well tolerated without any reported side effects or worsening of mood symptoms.

Safety

Adverse effects. No deaths or serious adverse effects occurred, and all reported adverse effects were mild and transient; no participants experienced moderate or severe adverse effects (see Table 2 for details). Gastrointestinal upset was alleviated by reminding affected participants to take EMP+ with food; likewise, occurrences of initial insomnia resolved on taking EMP+ earlier before bedtime.

Physical safety measures. Vital signs including temperature, heart rate, and blood pressure were within normal limits across all visits. Children gained weight and grew taller over the course of the study. Results of a series of nonparametric Wilcoxon signed rank tests showed no differences in BMI ($p = 0.310$) or WHR ($p = 0.674$) from pre- to postsupplementation (Table 3).

Blood assays

Table 4 contains pre- and postsupplementation concentrations of examined nutrients and their normal reference range for the seven participants completing the study. Serum concentrations of all nutrients were within normal ranges. Concentrations of four of the nutrients (vitamin A-retinol, vitamin B6, vitamin E-α-TC, and folate) significantly ($p < 0.05$) increased in response to supplementation with EMP$^+$. The increase in the serum concentration of 25-OH vitamin D from pre- to postsupplementation approached significance ($p = 0.063$). However, this increase appears to be driven by an outlier from one participant whose postsupplementation data were collected in early summer. Analyses of vitamin D after removal of this outlier no longer approached significance ($p = 0.116$). This suggests that changes in vitamin D may have been a result of environmental influences instead of EMP+ supplementation. There were no significant changes in serum concentrations of iron (sTfR or ferritin), magnesium, or zinc ($p > 0.05$). Decreases in γ-TC approached significance ($p = 0.063$). The two most abundant TCs in plasma, α- and γ-TC, were quantified to assess vitamin E status. It is unclear whether supplementation with α-TC decreases plasma levels of γ-TC. Although the mean plasma content of γ-TC decreased in response to supplementation with α-TC, the change was not statistically significant.

Exploratory correlations between micronutrient level changes and mood symptoms

Additional exploratory analyses found small to moderate positive correlations between changes in vitamin A (retinol) and depression score, change in serum vitamin B6 and depression score, and serum folate and global functioning. Small to moderate negative correlations were found for serum folate and depression and mania score, and serum vitamin A (retinol) and global functioning; however, none of these correlations reached statistical significance.

Nutritional outcomes

A series of nonparametric Wilcoxon signed rank tests revealed no significant differences in dietary intake on FFQ or 24hr from pre- to postsupplementation, suggesting that increases in serum concentrations of tested nutrients were caused by the intervention with the supplement (FFQ, $p < 0.088$ to $p < 0.963$; 24hr, $p < 0.095$ to

Table 4. Mean Serum Concentrations of Vitamins and Minerals Pre- and Post-EMP+ Supplementation

Nutrient	*Reference range*	*Average pre-EMP+ level Mean (SD)*	*Average post-EMP+ level Mean (SD)*	*Significance* (p)
sTfR	2.9–8.3 μg/mL	3.9 (0.82)	3.6 (0.46)	0.600
Ferritin	20.0–400.0 ng/mL	138.3 (104.31)	90.5 (69.97)	0.091
Mg	15.0–30.0 μg/mL	17.3 (1.02)	17.7 (0.49)	0.176
Zinc	> 0.8 μg/mL	1.7 (0.42)	1.8 (0.47)	0.612
Vit A: Retinol	> 0.70 μmol/L	3.3 (1.16)	5.0 (1.58)	0.018*
Vit B_6: PLP	20.0–120.0 nmol/L	54.3 (16.61)	104.0 (41.24)	0.028*
Vit D	> 20.0 ng/L	26.3 (3.93)	38.7 (22.22)	0.063
Vit E: α-TC	6–12 μg/mL	6.6 (2.07)	10.6 (3.00)	0.043*
Vit E: γ-TC	—-	1.3 (0.59)	0.92 (0.35)	0.063
Folate	3.8–23.2 μg/mL	3.9 (1.72)	5.9 (0.75)	0.028*

sTfR and ferritin are markers for iron status.

EMP+, EMPowerPlus; PLP, pyridoxal phosphate; α-TC, alpha tocopherol; γ-TC, gamma tocopherol; Mg, magnesium; sTfR, soluble transferrin receptor.

(−) not available; (*) significant, $p < 0.05$.

$p < 0.995$). Although there was a trend for increases in dietary vitamin B12 from pre- to postsupplementation based on the FFQ ($p = 0.06$), no notable trends were identified from the 24hr.

Discussion

This small open-label trial provides preliminary data suggesting that EMP+ may be safe in children ages 6–12 with BPSD not taking mood stabilizing medications. It is also the first to report pre-post changes in serum concentrations of vitamins and minerals controlled for by dietary intake. These results support the feasibility for a double-blind, placebo-controlled study of EMP+ in children with BPSD.

Although frank micronutrient deficiencies are generally assumed to be infrequent in developed countries, more recent data indicate a relatively high prevalence of vitamin D deficiency in child and adult populations with depression and psychosis (Gracious et al. 2012; Tolppanen et al. 2012). Vitamin B12 deficiency is classically known to be related to psychosis. Diet quality is linked to better mental health outcomes epidemiologically in adolescents and adults (Jacka et al., 2011a,b). The possibility that supplementation with EMP+ offsets one or more defects in absorption, tissue distribution, cellular metabolism, or whole body retention of selected vitamins and minerals merits ongoing consideration and testing. Such problems may result from subtle mutations or allelic variation in gene expression for enzyme production, such as in those with tetrahydrofolate variants (Ellingrod et al. 2008).

Effects on inflammation and relation to mood changes

Micronutrient effects on CNS processes that contribute to mood symptoms have not been adequately investigated. Potential mechanisms of action for relevant nutrients found in the EMP+ supplement are described subsequently.

Iron. Serum ferritin and soluble transferrin receptor were used as biomarkers for possible inflammation and iron status. Elevated serum ferritin has been associated with melancholic major depressive disorder, induced by corresponding inflammatory-immune changes (Maes et al. 1996). Our patients showed a decreasing trend in serum ferritin and no significant change in sTrR, which is consistent with the proposed anti-inflammatory activity for EMP+ and not a reduction in iron status, as the soluble transferrin receptor is a better measure of body iron stores than ferritin. The iron content in 15 capsules of EMP+ (as chelate) is <100% of the recommended daily value; therefore, excessive intake is unlikely.

Vitamin A. Vitamin A deficiency remains a widespread public health problem in rural areas of developing nations, and predominantly affects pregnant women and preschool children. This condition contributes to night blindness, loss of eyesight, and early mortality from infectious diseases, especially measles (National Institutes of Health Office of Dietary Supplements 2012). A highly grain-based diet, without animal products (including dairy) or fruit and vegetable supplementation, contributes to this deficiency. Retinyl palmitate (384 IU per capsule) is the vitamin A component of EMP+. Administration of 15 capsules per day (5760 IU) does not exceed the tolerable upper intake limit of 9333 IU per daily (ULs) for preformed vitamin A. However, as a fat-soluble vitamin with potential to contribute to cancer, decreased bone mass, pseudotumor cerebri, and congenital birth defects (Institute of Medicine 2001), caution is recommended for chronic intake. A summary of neuropsychiatric presentations related to vitamin A toxicity is presented in a review of isoretinoids and affective disorders (Bremner et al. 2012), including mechanisms involving retinoic acid signaling in the hypothalamus that contributes to overactivity of the HPA axis via corticotropin-releasing hormone. Vitamin A may also contribute to an increase in oxidative stress in the CNS; animal models have shown tissue concentration in the CNS is greater than that in serum (de Oliveira et al. 2008).

Pyridoxine (Vitamin B6). Vitamin B6 (pyridoxine) is an essential cofactor required for the re-methylation of homocysteine to cysteine. Folate status also affects serum homocysteine, and together with vitamin B6 modulates serotonin and catecholamines, which are important transmitters in mood disorders. B6, as the active form pyridoxal-6-phosphate, is a coenzyme for production of serotonin. However, this study found no evidence directly linking the increased concentration of serum vitamin B6 after EMP+ supplementation with improvements in mood or psychotic symptoms. In fact, there was a negative correlation between increased pyridoxine blood concentration and mood and global improvement, possibly from a speculative enzyme or coenzyme deficiency for conversion of supplemented pyridoxine to the active PLP, resulting in a hypothesized ''backup'' of pyridoxine. This speculation could be examined in a future study (Malouf and Grimley Evans 2003). Vitamin B6 is an understudied micronutrient in terms of its effect on mood disorders, especially as vitamin B6 deficiency does occur clinically.

Vitamin D. Vitamin D deficiency is associated with depression and psychosis in epidemiologic samples (Bertone-Johnson 2009; Berg et al. 2010). Vitamin D is neuroprotective to hippocampal cells, regulating calcium ion channels and activating protein kinase C (PKC) and mitogen-activated protein kinase (maPK) pathways (McCann and Ames 2008). Mean serum concentration of 25-OH vitamin D was at the lower limit of adequacy at baseline. Initially, changes in vitamin D in the current sample approached a significant increase over the 8 week trial. However, the post-supplementation data from one participant who ended the study in the summer created an outlier that appeared to be driving the trend toward significance in pre- to postsupplementation changes in vitamin D. When analyzed after removing this outlier, changes in vitamin D no longer approached significance. This suggests that environmental factors, including increased sun exposure in the summer, may have contributed to the increase in vitamin D. However, because of the single instance of this result, conclusions regarding whether or not EMP+ raised serum concentrations of vitamin D in this study remain unclear. Daily intake of 1440 IU of cholecalciferol (vitamin D3) total from the 15 capsules per day exceeds the current recommended daily allowance (RDA) of 600 IU for individuals 1–70 years of age (Ross et al. 2011), but is below levels that have been reported to be safe for adolescents given supplementation for up to 1 year (Maalouf et al. 2008; Arpadi et al. 2009).

Vitamin E. Vitamin E, as α-TC, has antioxidant properties and anti-inflammatory effects within lipid-rich membranes. α-TC reduces both prostaglandin-E2 production by macrophages and pro-inflammatory cytokine synthesis and secretion by activated macrophages and monocytes (Capuron et al. 2009). γ-TC also reduces prostaglandin E2 synthesis by even greater inhibition in cyclooxygenase (COX)-2 activity in macrophages, as well as reducing COX-2 activity in epithelial cells (Jiang et al. 2000). Safety data and dosing for vitamin E is as yet unclear for different human

populations. A U-shaped dose response curve may exist for the anti-inflammatory effects of γ-TC, with implications for safety (McCary et al. 2011). The dose of α-TC in EMP+ as recommended (360 IU total from 15 capsules per day) is lower than that shown to be safe and effective in a small RCT in children with immunoglobulin (Ig)A nephropathy (400 or 800 IU/day, respectively for body weights of <30 kg or >30 kg; Chan et al. 2003), but significantly more than the United States RDA (http://ods.od.nih.gov/factsheets/VitaminE-HealthProfessional/). Concern about differential responses to vitamin E supplementation in children versus adults and healthy versus chronic disease status exists. Adult vitamin E supplementation study findings have shown an increase in all-cause mortality (meta-analysis; Miller et al. 2005), a greater rate of cognitive decline in those with Alzheimer's disease (Galasko et al. 2012), and a trend toward new cases of prostate cancer in men (Klein et al. 2011). Thabet et al. (2006) cite other studies including meta-analyses that did not confirm these concerns, providing data supporting safety of vitamin E for renal disease patients, especially in children. Response versus worsening may depend upon the presence and degree of oxidative stress present, at least for those with Alzheimer's disease (Lloret et al. 2009). Also, a coantioxidant may be necessary to reduce α-TC after oxidation to prevent generation of lipid radicals (Thabet et al. 2006). Further study of the effects of supplemental vitamin E on brain function and illness are needed before it can be considered useful and/or safe in all populations and ages.

Folic acid (vitamin B9). Folate deficiency is present in up to 50% of those with depression (Alpert and Fava 1997), and genetic variants associated with reduced folate metabolism result in inflammation and elevated homocysteine levels, which can reduce the concentrations of the neurotransmitters serotonin, norepinephrine, and dopamine (Bottiglieri 2000). Adjunctive L-methyl folate has recently been shown to be helpful in adults with treatment-resistant depression (Papakostas et al. 2012). Participant serum concentrations of folate in our study were either deficient or close to deficient at baseline, an unexpected finding, given that grain product fortification with folic acid was mandated in the United States effective January 1, 1998 (Oakley et al. 1996). Patients with bipolar disorder who are taking valproic acid, which is an inhibitor of folic acid absorption, are more likely to be folate deficient. Serum folate concentrations increased in response to supplementation with EMP+, although they were still below those reported for children taking vitamin supplements (Bailey et al. 2012). This change was associated with a trend toward decreasing depression and small to moderate improvements in global functioning, indicating that folate may be a potential adjuvant for the treatment of BPSD. Intake of 1440 μg supplemental folic acid in 15 capsules of EMP+ merits further consideration, as this amount is higher than that in most folic acid supplements. The United States reference daily intake (RDI) is 300 μg for children ages 9–13 years and 200 μg per day for children ages 4–8 years (Institute of Medicine 1998). As folate is water soluble, it is generally considered to be nontoxic, but a caution exists. In adults, doses >1 g/day of folic acid may mask vitamin B12 deficiency (Institute of Medicine 1998). Combining folic acid with vitamin B12 in supplements is generally assumed to offset such risk. Daily intake of vitamin B12 in 15 capsules of EMP+ is 900 μg, well above the dietary reference intake (DRI) for men and women of 2–3 μg per day. Vitamin B12 supplementation (given in EMP+ as cyanocobalamin) is generally considered safe in higher doses except for those who may have undiagnosed conditions of megaloblastic anemia or hereditary optic atrophy. Therefore, a complete blood count and excluding for optic atrophy could be justified before recommending supplementation with EMP+, although these conditions in children may be extremely rare in the United States.

Prostaglandin and eicosanoid modulation effects

EMP+ may also decrease inflammation by reducing synthesis of prostaglandin E2 and other series 2 icosanoids derived from arachidonic acid. Effects of omega-3 fatty acids with and without psychoeducational psychotherapy in children with depression or BP-NOS are currently under study by our group. A logical next step might be to test whether omega-3 fatty acids and EMP+ micronutrients have an additive effect, and whether they may be addressing a metabolic inflammatory imbalance from different entry points.

Individual variations in nutrition

Optimal nutritional status requires detailed clinical, biochemical, dietary, and anthropometric information to define the personal needs of an individual (Kaplan et al. 2007). Ubiquitous individual and familial genetic variations that affect nutrient metabolism add to the complexity of defining optimal nutrition for any individual. Methods to accurately assess how different amounts of nutrients directly affect brain function are lacking. Analyses used in this study examined serum concentrations of various nutrients from participants as indicators of dietary intake and peripheral metabolism as opposed to nutrient concentrations and activity in the CNS. The data suggest that supplementation was associated with increased concentrations of serum vitamins A-retinol, B6, E (α-TC), and folate. Exploratory analyses showed variable correlations between changes in these nutrient blood levels and some changes in mood and global functioning scores that are not interpretable at this time, because of the small sample size and lack of power. Collectively, these trends illustrate the limitations of a very small open feasibility sample, and our limited understanding of vitamin and mineral nutrition and the biochemistry of the brain.

Conclusions

These preliminary results are the first to report impact of daily supplementation on serum micronutrient measures, and add to the support for further investigation of EMP+. A larger double-blind RCT in youth with BPSD appears feasible, and is warranted by the encouraging open clinical outcomes of this 8 week open study, which include the ability of the supplement to increase serum concentrations of certain nutrients with limited transient side effects reported. Future studies of EMP+ will ideally use functional biomarkers and imaging techniques to better understand how changes in intake of various nutrients may affect CNS functioning and mood states; maintenance studies will determine long-term safety. It may be ultimately that individualized nutrient supplementation is optimal based on detectable genetic variations in micronutrient metabolism, including receptor or transcription factors.

Clinical Significance

Increasing evidence illustrates the important role that micronutrients play in both physical and mental health. Current psychotropic medications for childhood BPSD are associated with significant adverse events, and treatments with a more acceptable risk–benefit ratio are sorely needed. Multinutrient supplement

interventions may be useful in treating pediatric mood disorders with few side effects. The current investigations explores the safety, tolerability, and serum micronutrient concentrations and their correlations with mood changes from an 8 week pilot feasibility study of a 36 ingredient multinutrient supplement, EMP+, for pediatric BPSD. Results showed that EMP+ appeared safe and well tolerated, with a side effect profile preferable to that of first-line psychotropic drugs for pediatric BPSD, suggesting that further more rigorous scientific study is needed to determine if EMP+ continues to show a more preferable risk–benefit ratio when compared with placebo in an RCT.

Acknowledgments

We thank Sue Thompson, NP, for completing physical examinations, and the dietitians and nurses at the Ohio State Clinical Research Center for completing dietary monitoring and blood draws throughout this study.

Disclosures

Dr. Arnold has/had research funding from Autism Speaks, Curemark, the National Institute for Mental Health (NIMH), Neuropharm, Novartis, Noven, Shire, Sigma Tau, and Targacept; has consulted for Abbott, Biomarin, Neuropharm, Novartis, Noven, Organon, Shire, and Sigma Tau; and was a speaker for McNeil, Novartis, and Shire. Dr. Fristad receives royalties from American Psychiatric Publishing, Inc. (APPI), Guilford Press and CFPSI. Dr. Gracious has been a consultant to Johnson and Johnson. Drs. Frazier, Habash, Failla, and Chitchumroonchokchai have no conflict of interest or financial ties to disclose.

References

Alpert JE, Fava M: Nutrition and depression: The role of folate. Nutr Rev 55:145, 1997.

Ambrosini PJ, Metz C, Prabucki K, Lee JC: Videotape reliability of the third revised edition of the K-SADS. J Am Acad Child Adolesc Psychiatry 28:723–728, 1989.

American Psychiatric Association: Diagnostic and Statistical Manual of Mental Disorders, 4th ed., Text Revision. Washington, DC: American Psychiatric Association, 2000.

Arpadi SM, McMahon D, Abrams EJ, Bamji M, Purswani M, Engelson ES, Horlick M, Shane E: Effect of bimonthly supplementation with oral cholecalciferol on serum 25-hydroxyvitamin D concentrations in HIV-infected children and adolescents. Pediatrics 123:121–126, 2009.

Axelson D, Birmaher BJ, Brent D, Wassick S, Hoover C, Bridge J, Ryan N: A preliminary study of the Kiddie Schedule for Affective Disorders and Schizophrenia for School-Age Children Mania Rating Scale for Children and Adolescents. J Child Adolesc Psychopharmacol 13:463–470, 2003.

Bailey RL, Fulgoni VL 3rd, Keast DR, Lentino CV, Dwyer JT: Do dietary supplements improve micronutrient sufficiency in children and adolescents? J Pediatr 161:837–842, 2012.

Benton D: The influence of children's diet on their cognition and behavior. Eur J Nutr 47:25–37, 2008.

Berg AO, Melle I, Torjesen PA, Lien L, Hauff E, Andreassen OA: A cross-sectional study of vitamin D deficiency among immigrants and Norwegians with psychosis compared to the general population. J Clin Psychiatry 71:1598–1604, 2010.

Bertone–Johnson ER: Vitamin D and the occurrence of depression: Causal association or circumstantial evidence? Nutr Rev 67:481–492, 2009.

Bottiglieri T: Homocysteine and folate metabolism in depression. Prog Neuropsychopharmacol Biol Psychiatry 29:1103–1112, 2005.

Bremner JD, Shearer KD, McCaffery PJ: Retinoic acid and affective disorders: The evidence for an association. J Clin Psychiatry 73:37–50, 2012.

Capuron L, Moranis A, Combe N, Cousson–Gélie F, Fuchs D, De Smedt–Peyrusse V, Barberger–Gateau P, Layé S: Vitamin E status and quality of life in the elderly: Influence of inflammatory processes. Br J Nutr 102:1390– 1394, 2009.

Chambers WJ, Puig–Antich J, Hirsch M, Paez P, Ambrosini PJ, Tabrizi MA, Davies M: The assessment of affective disorders in children and adolescents by semistructured interview: Test–retest reliability of the Schedule for Affective Disorders and Schizophrenia for School-Age Children, Present Episode Version. Arch Gen Psychiatry 42:696–702, 1985.

Chan JCM, Mahan JD, Trachtman H, Scheinman J, Flynn JT, Alon US, Lande MB, Weiss RA, Norkus EP: Vitamin E therapy in IgA nephropathy: A double-blind, placebo-controlled study. Pediatr Nephrol 18:1015–1020, 2003.

Conway JM, Ingwersen LA, Vinyard BT, Moshfegh AJ: Effectiveness of US Department of Agriculture 5-step multiple-pass method in assessing food intake in obese and nonobese women. Am J Clin Nutr 77:1171–1178, 2003.

Cook JD, Skikne BS, Baynes RD: Serum transferrin receptor. Annu Rev Med 44:63–74, 1993.

Correll CU, Manu P, Olshanskiy V, Napolitano B, Kane JM, Malhotra AK: Cardiometabolic risk of second-generation antipsychotic medications during first-time use in children and adolescents. JAMA 302:1765–1773, 2009.

de Oliveira MR, Silvestrin RB, Mello e Souza T, Moreira JC: Therapeutic vitamin A doses increase the levels of markers of oxidative insult in substantia nigra and decrease locomotory and exploratory activity in rats after acute and chronic supplementation. Neurochem Res 33:378–383, 2008.

Ellingrod VL, Miller DD. Taylor SF, Moline J, Holman T, Kerr J: Metabolic syndrome and insulin resistance in schizophrenia patients receiving antipsychotics genotyped for the methylenetetrahydrofolate reductase (*MTHFR*) 677C/T and 1298A/C variants. Schizophrenia Res 98:47–54, 2008.

Fleischhaker C, Heiser P, Hennighausen K, Herpertz-Dahlmann B, Holtkamp K, Mehler-Wex C, Rauh R, Remschmidt H, Schulz E, Warnke A: Clinical drug monitoring in child and adolescent psychiatry: Side effects of atypical neuroleptics. J Child Adolesc Psychopharmacol 16:308–316, 2006.

Frazier EA, Fristad MA, Arnold LE: Feasibility of a nutritional supplement as treatment for pediatric bipolar spectrum disorders. J Altern Complement Med 18:678–685, 2012.

Frazier EA, Fristad MA, Arnold LE: Micronutrient supplement as treatment: Literature review and case report of a 12-year-old boy with bipolar disorder. J Child Adolesc Psychopharmacol 19:453–460, 2009.

Galasko DR, Peskind E, Clark CM, Quinn JF, Ringman JM, Jicha GA, Cotman C, Cottrell B, Montine TJ, Thomas RG, Aisen P: For the Alzheimer's Disease Cooperative Study. Antioxidants for Alzheimer disease: A randomized clinical trial with cerebrospinal fluid biomarker measures. Arch Neurol 69:836–841, 2012.

Gracious B, Finucane TL, Freidman–Campbell M, Messing S, Parkhurst MM: Vitamin D deficiency and psychotic features in mentally ill adolescents: A cross-sectional study. BMC Psychiatry 12:38, 2012.

Halliwell C, Kolb B: Diet can stimulate functional recovery and cerebral plasticity after perinatal cortical injury in rats. Soc Neuro Abs 29:459.411, 2003.

Institute of Medicine, Food and Nutrition Board: Dietary Reference Intakes: Thiamin, Riboflavin, Niacin, Vitamin B6, Folate, Vitamin

B12, Pantothenic Acid, Biotin, and Choline. Washington, DC: National Academy Press, 1998.

Institute of Medicine, Food and Nutrition Board: Dietary Reference Intakes for Vitamin A, Vitamin K, Arsenic, Boron, Chromium, Copper, Iodine, Iron, Manganese, Molybdenum, Nickel, Silicon, Vanadium, and Zinc. Washington, DC: National Academy Press, 2001.

Jacka FN, Kremer PJ, Berk M, de Silva–Sanigorski AM, Moodie M, Leslie ER, Pasco JA, Swinburn BA: A prospective study of diet quality and mental health in adolescents. PLoS One 6: e24805, 2011a.

Jacka FN, Mykletun A, Berk M, Bjelland I, Tell GS: The association between habitual diet quality and the common mental disorders in community-dwelling adults: The Hordaland Health study. Psychosom Med 73:483–490, 2011b.

Jiang Q, Elson–Schwab I, Courtemanche C, Ames BN: γ-tocopherol and its major metabolite, in contrast to α-tocopherol, inhibit cyclooxygenase activity in macrophages and epithelial cells. Proc Nat Acad Sci U S A 97:11,494–11,499, 2000.

Kaplan BJ, Crawford SG, Field CJ, Simpson JS: Vitamins, minerals, and mood. Psychol Bull 133:747–760, 2007.

Kaplan BJ, Crawford SG, Gardner B, Farrelly G: Treatment of mood lability and explosive rage with minerals and vitamins: Two case studies in children. J Child Adolesc Psychopharmacol 12:205–219, 2002.

Kaplan BJ, Fisher JE, Crawford SG, Field CJ, Kolb B: Improved mood and behavior during treatment with a mineral-vitamin supplement: An open-label case series of children. J Child Adolesc Psychopharmacology 14:115–122, 2004.

Kaplan BJ, Simpson SA, Ferre RC, Gorman CP, McMullen DM, Crawford SG: Effective mood stabilization with a chelated mineral supplement: An open-label trial in bipolar disorder. J Clin Psychiatry 62:936–944, 2001.

Klein EA, Thompson IM Jr, Tangen CM, Crowley JJ, Lucia MS, Goodman PJ, Minasian LM, Ford LG, Parnes HL, Gaziano JM, Karp DD, Lieber MM, Walther PJ, Klotz L, Parsons JK, Chin JL, Darke AK, Lippman SM, Goodman GE, Meyskens FL Jr, Baker LH: Vitamin E and the risk of prostate cancer: The Selenium and Vitamin E Cancer Prevention Trial (SELECT). JAMA 306:1549–1556, 2011.

Kowatch RA, Fristad M, Birmaher B, Wagner KD, Findling RL, Hellander M, Child Psychiatric Workgroup on Bipolar Disorder: Treatment guidelines for children and adolescents with bipolar disorder: Child psychiatric workgroup on bipolar disorder. J Am Acad Child Adolesc Psychiatry 44:213–235, 2005.

Kowatch RA, Fristad MA, Findling RL, Post RM: A Clinical Manual for the Management of Bipolar Disorder in Children and Adolescents. Arlington, VA: American Psychiatric Press, Inc, 2009.

Lloret A, Badía MC, Mora NJ, Pallardó FV, Alonso MD, Viña J: Vitamin E paradox in Alzheimer's disease: It does not prevent loss of cognition and may even be detrimental. J Alzheimers Dis 17: 143–149, 2009.

Maalouf J, Nabulsi M, Vieth R, Kimball S, El-Rassi R, Mahfoud Z, Fuleihan GEH: Short- and long-term safety of weekly high-dose vitamin D3 supplementation in school children. J Clin Endocrinol Metab 93:2693–2701, 2008.

Maes M, Van De Vyvere J, Vandoolaeghe E, Bril T, Demedts P, Wauters A, Neels H: Alterations in iron metabolism and the erythron in major depression: Further evidence for a chronic inflammatory process. J Affect Disord 40:23–33, 1996.

Malouf R, Grimley Evans J: The effect of vitamin B6 on cognition. Cochrane Database Syst Rev 4:CD004393, 2003.

McCann J, Ames B: Is there convincing biological or behavioral evidence linking vitamin D deficiency to brain dysfunction? FASEB J 22:982–1001, 2008.

McCary CA, Abdala–Valencia H, Berdnikovs S, Cook–Mills JM: Supplemental and highly elevated tocopherol doses differentially regulate allergic inflammation: reversibility of α-tocopherol and γ-tocopherol's effects. J Immunol 186:3674–3685, 2011.

McIntyre, RS, Jerrell, JM: Metabolic and cardiovascular adverse events associated with antipsychotic treatment in children and adolescents. Arch Pediatr Adolesc Med 162:929–935, 2008.

Mehl-Madrona L, Leung B, Kennedy C, Paul, S, Kaplan, BJ: Micronutrients versus standard medication management in autism: A naturalistic case-control study. J Child Adolesc Psychopharmacol 20:95–103, 2010.

Miller III ER, Pastor–Barriuso R, Dalal D, Riemersma RA, Appel LJ, Guallar E: Meta-analysis: high-dosage vitamin E supplementation may increase all-cause mortality. Ann Intern Med 142:37–46, 2005.

National Institute of Mental Health: Clinical Global Impressions Scale. Psychopharm Bul 21: 839–843, 1985.

National Institutes of Health Office of Dietary Supplements: Dietary supplement fact sheet: Vitamin A. Accessed 13 August 2012 at http://ods.od.nih.gov/factsheets/VitaminA-HealthProfessional, 2012.

Nutrition Data System for Research (Manual), Nutrition Coordinating Center University of Minnesota, Minneapolis, MN, 55454-1015; Appendix 10; Food Groupings: 10.1–10.11, 2005a.

Nutrition Data System for Research (Manual), Nutrition Coordinating Center University of Minnesota, Minneapolis, MN, 55454-1015; Appendix 22; Sources of Nutrient Data: A22.1–A22.12, 2005b.

Oakley GP, Jr., Adams MJ, Dickinson CM: More folic acid for everyone, now. J Nutr 126:751S–755S, 1996.

Papakostas GI, Shelton RC, Zajecka JM, Etemad B, Rickels K, Clain A, Baer L, Dalton ED, Sacco GR, Schoenfeld D, Pencina M, Meisner A, Bottiglieri T, Nelson E, Mischoulon D, Alpert JE, Barbee JG, Zisook S, Fava M: l-Methylfolate as adjunctive therapy for SSRI-resistant major depression: Results of two randomized, double-blind, parallel-sequential trials. Am J Psychiatry 169:1267–1274. 2012.

Podda M, Weber C, Traber MG, Packer L: Simultaneous determination of tissue tocopherols, tocotrienols, ubiquinols and ubiquinones. J Lipid Res 37:893, 1996.

Popper CW. Do vitamins or minerals (apart from lithium) have mood–stabilizing effects? J Clin Psychiatry 62:933–935, 2001.

Ross AC, Taylor CL, Yaktine AL, Del Valle HB: Committee to Review Dietary Reference Intakes for Vitamin D and Calcium; Institute of Medicine. Washington, DC: The National Academies Press, 2011.

Rucklidge JJ: Successful treatment of OCD with a micronutrient formula following partial response of cognitive behavioral therapy (CBT): A case study. J Anxiety Disord 23:836–840, 2009.

Rucklidge J, Harrison R: Successful treatment of bipolar disorder II and ADHD with a micronutrient formula: A case study. CNS Spectr 15:231–237, 2010.

Rucklidge J, Taylor M, Whitehead K: Effect of micronutrients on behavior and mood in adults with ADHD: Evidence from an 8-week open label trial with natural extension. J Atten Disord 13: 1–13, 2010.

Shaffer D, Gould MS, Brasic J, Ambrosini P, Fisher P, Bird H, Aluwahlia S: A Children's Global Assessment Scale (CGAS). Arch Gen Psychiatry 40:1228–1231, 1983.

Shaole W, Feng X, Wittmeier A: Microwave digestion of plant and grain reference materials in nitric acid or a mixture of nitric acid or a mixture of nitric acid and hydrogen peroxide for the determination of multi-elements by inductively coupled plasma mass spectrometry. J Anal At Spectrom 12:797–806, 1997.

Shils ME, Shike M, Ross AC, Caballero B, Cousins RJ: Modern Nutrition in Health and Disease, 10th ed. Baltimore: Lippincott, Williams and Wilkins, 2006.

Simmons M: Nutritional approach to bipolar disorder. J Clin Psychiatry 64:338, 2003.

Simpson JSA, Crawford SG, Goldstein ET, Field C, Burgess E, Kaplan BJ: Safety and tolerability of a complex micronutrient formula used in mental health: A compilation of eight datasets. BMC Psychiatry 11:62, 2011.

Thabet MA, Chan JCM: Vitmain E in renal therapeutic regimens. Pediatr Nephrol 21:1790–1801, 2006.

Tolppanen AM, Sayers A, Fraser WD, Lewis G, Zammit S, Lawlor DA: The association of serum 25-hydroxyvitamin D3 and D2 with depressive symptoms in childhood – A prospective cohort study. J Child Psychol Psychiatry 53:757–766, 2012.

Vazquez–Lopez MA, Carracedo A, Lendinez F, Munoz FJ, Lopez J, Munoz A: The usefulness of serum transferrin receptor for discriminating iron deficiency without anemia in children. Haematologia 91:264, 2006.

Weber JL, Lytle, L, Gittelsohn, J, Cunningham–Sabo, L, Heller K, Anliker, JA, Stevens J, Hurley J, Ring K: Validity of self-reported dietary intake at school meals by American Indian children: The pathways study. J Am Diet Assoc 104:746–752, 2004.

Wilson AMR, Lewis RD: Disagreement of energy and macronutrient intakes estimated from a food frequency questionnaire and 3-day diet record in girls 4 to 9 years of age. J Am Diet Assoc 104:373–378, 2004.

World Health Organization: Iron Deficiency Anemia: Assessment, Prevention and Control. A Guide for Programme Managers. Document WH/NDH/01.3, 2001.

Address correspondence to:
Elisabeth Frazier, PhD
49 Berwick Lane
Cranston, RI 02905

E-mail: elisabeth_frazier@brown.edu