Archival Report

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The Vitamins in Psychosis Study: A Randomized, Double-Blind, Placebo-Controlled Trial of the Effects of Vitamins B_{12}, B_6, and Folic Acid on Symptoms and Neurocognition in First-Episode Psychosis

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ABSTRACT

BACKGROUND: Elevated homocysteine is observed in schizophrenia and associated with illness severity. The aim of this study was to determine whether vitamins B_{12}, B_6, and folic acid lower homocysteine and improve symptomatology and neurocognition in first-episode psychosis. Whether baseline homocysteine, genetic variation, sex, and diagnosis interact with B-vitamin treatment on outcomes was also examined.

METHODS: A randomized, double-blind, placebo-controlled trial was used. A total of 120 patients with first-episode psychosis were randomized to an adjunctive B-vitamin supplement (containing folic acid [5 mg], B_{12} [0.4 mg], and B_6 [50 mg]) or placebo, taken once daily for 12 weeks. Coprimary outcomes were change in total symptomatology (Positive and Negative Syndrome Scale) and composite neurocognition. Secondary outcomes included additional measures of symptoms, neurocognition, functioning, tolerability, and safety.

RESULTS: B-vitamin supplementation reduced homocysteine levels (p = .003, effect size = −0.65). B-vitamin supplementation had no significant effects on Positive and Negative Syndrome Scale total (p = .749) or composite neurocognition (p = .785). There were no significant group differences in secondary symptom domains. A significant group difference in the attention/vigilance domain (p = .024, effect size = 0.49) showed that the B-vitamin group remained stable and the placebo group declined in performance. In addition, 14% of the sample had elevated baseline homocysteine levels, which was associated with greater improvements in one measure of attention/vigilance following B-vitamin supplementation. Being female and having affective psychosis was associated with improved neurocognition in select domains following B-vitamin supplementation. Genetic variation did not influence B-vitamin treatment response.

CONCLUSIONS: While 12-week B-vitamin supplementation might not improve overall psychopathology and global neurocognition, it may have specific neuroprotective properties in attention/vigilance, particularly in patients with elevated homocysteine levels, patients with affective psychosis, and female patients. Results support a personalized medicine approach to vitamin supplementation in first-episode psychosis.

Keywords: Attention, B vitamins, Early psychosis, Folic acid, Genetics, Homocysteine

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Homocysteine is a sulfur amino acid that is synthesized from methionine, and its regulation depends on dietary intake of folic acid and B vitamins (1). Elevated homocysteine levels and severe deficiencies in folate and B vitamins are risk factors for neurodevelopmental problems, heart disease, stroke, cognitive decline, and mood disorders (2–4). Elevated prenatal homocysteine has been associated with a twofold increased risk for schizophrenia (5). Blood levels of homocysteine are also elevated in people with schizophrenia, and higher levels of homocysteine are associated with younger age (1,6). These elevated homocysteine levels are observed from illness onset in patients with first-episode psychosis (FEP), independent of antipsychotic medication (7,8). Furthermore, elevated homocysteine has been associated with higher negative symptomatology (9,10) and poorer functioning (11). The relationships between clinical disease presentation and higher levels of homocysteine suggest that reducing homocysteine levels may be therapeutic in schizophrenia. One method to achieve this is folate supplementation.

Impairments in folate metabolism can cause adverse consequences for genome structure, expression, and stability and can result from folate deficiency, secondary nutrient

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deficiencies (vitamins B_6 and B_{12} and iron), and single nucleotide polymorphisms in folate-dependent enzymes. A recent meta-analysis examining blood nutrient levels of vitamins in FEP found significant deficits in folate compared with healthy control subjects (Hedges' $g = -0.624$) (12). Furthermore, lower folate levels were associated with more severe negative symptoms (12). In humans, several common single nucleotide polymorphisms regulate folate. The 677C>T variant in the methylenetetrahydrofolate reductase gene, *MTHFR*, has been the most studied polymorphism in schizophrenia (6,13,14). Meta-analytic findings have shown an association between homozygosity of the 677C>T polymorphism in the *MTHFR* gene and schizophrenia, potentially suggesting a causal relationship between aberrant homocysteine metabolism and genotype (1,6). The 677C>T *MTHFR* polymorphism is associated with variation in negative symptom severity in long-term schizophrenia (14). Missense variants in methionine synthase (*MTR* 2756A), folate hydrolase 1 (*FOLH1* 484C), and catechol-*O*-methyltransferase (*COMT* 675A) have also been shown to be predictive of negative symptom severity (15). These findings further support the hypothesis that folate supplementation may be beneficial in schizophrenia.

Multiple randomized controlled trials (RCTs) have investigated the effects of homocysteine-lowering agents (e.g., folic acid, vitamins B_{12} and B_6) on clinical outcomes in long-term schizophrenia. An early study showed that 6-month L-methylfolate (15 mg) administration in patients with folate deficiency significantly reduced symptomatology compared with placebo (16). A larger study of 12 weeks of L-methylfolate (15 mg) in individuals with schizophrenia recently replicated these findings, showing moderate to large reductions in total, general, and negative symptomatology (17). Findings were moderated by folate-related genetic variation (17). Other RCTs using combined B-vitamin supplements have revealed various benefits, including significant decreases in homocysteine levels, total psychopathology and cognitive deficits (7), and reduced negative symptoms specifically in people homozygous for the 484T allele in the 484C>T variant of *FOLH1* (13). A recent meta-analysis of data pooled from seven B-vitamin RCTs in schizophrenia found a moderate positive effect (Hedges' $g = 0.51$) of vitamin supplementation on total symptom levels (18). Studies that used a combination of B vitamins were most effective, and effectiveness was associated with shorter illness duration (18). However, no study has investigated the effectiveness of B vitamins in FEP.

The main aim of this study was to investigate prospectively the effects of vitamin B_{12}, B_6, and folic acid supplementation on symptom and neurocognitive outcomes in patients with FEP. The hypothesis was that compared with placebo, patients with FEP treated with adjuvant B vitamins for 12 weeks would experience a reduction in plasma homocysteine levels and improvements in psychiatric symptoms and neurocognition. We also explored whether elevated baseline homocysteine (>15 μmoL/L), genetic variants within the folate metabolic pathway (*FOLH1* 484C>T, *MTHFR* 677C>T, *MTR* 1298G>A, and *COMT* 675G>A), sex, and diagnosis were associated with change in psychiatric symptoms and neurocognition following B-vitamin supplementation.

METHODS AND MATERIALS

Design

This was a parallel, double-blind, randomized, placebo-controlled study investigating the efficacy of vitamin B_{12}, B_6, and folic acid supplementation in individuals with FEP. The study was approved by the NorthWestern Health Care Network Research and Ethics Committee of Melbourne Health (Melbourne, Australia). Participant recruitment occurred from September 2004 to June 2006. All participants provided written consent, including parental/guardian consent for those <18 years old. The trial is registered with ClinicalTrials.gov (No. NCT00202280).

Sample

People receiving outpatient treatment for a FEP at the Early Psychosis Prevention and Intervention Centre (EPPIC), a subprogram of Orygen Youth Health in Melbourne, Australia, were eligible to participate. The Early Psychosis Prevention and Intervention Centre is a specialized public mental health service for people aged 15 to 25 years in metropolitan Melbourne who have experienced a first episode of psychosis (19).

After giving informed consent, participants completed the Structured Clinical Interview for DSM (20) to confirm psychotic disorder. In cases in which Structured Clinical Interview for DSM was not completed, diagnosis was obtained by psychiatric interview, review of medical records, and clinician consultation. Patients were included if they met criteria for a DSM-IV (21) psychotic disorder, including schizophrenia; schizophreniform, schizoaffective, or delusional disorder; major depression or bipolar disorder with psychotic features; or psychosis not otherwise specified.

Exclusion criteria included <3 months of treatment or floridly psychotic presentation; IQ < 80; history of clinically significant physical illness, brain surgery, infarction, or neurological impairment (e.g., brain tumor, epilepsy); hypersensitivity to folic acid; untreated vitamin B_{12} deficiency or pernicious anemia, thalassemia major, or sickle-cell anemia; or if already taking multivitamin supplements, vitamin B_6, or folic acid unless willing to discontinue. Women who were pregnant, lactating, or not using contraception were also excluded.

Randomization and Masking

Consented participants were randomized to either a single tablet of vitamins (folic acid [5 mg], vitamin B_{12} [0.4 mg], and vitamin B_6 [50 mg]) or placebo once daily for 12 weeks. Given that the mechanism of focus for this trial was to reduce homocysteine, folate rather than methylfolate was chosen because this was most commonly used in previous trials of homocysteine reduction (22,23). All participants continued to receive standard Early Psychosis Prevention and Intervention Centre treatment throughout the trial, including case management and atypical antipsychotic and other medication as prescribed by their doctor. Participants were randomized by a dynamic randomization method called minimization that allocates patients to treatment group by taking into account the allocation of similar patients already randomized and allocating the next treatment group live to best balance the treatment groups across stratification variables (24–26). Stratification

variables included sex (male or female), diagnosis (affective or nonaffective psychosis), concomitant medication (aripiprazole or other), and age (≤18 or >18 years). Randomization was conducted off-site independent of the study team at the National Health and Medical Research Council Clinical Trials Centre (Sydney, Australia). Randomization codes were sent to the off-site clinical trials pharmacy that dispensed either B vitamins or placebo to participants to ensure allocation concealment. All study personnel, including the participants, treating team, statistician, investigators, and assessors, were blinded to treatment assignment for the study duration.

Assessment Instruments

Sociodemographic data were recorded. The National Adult Reading Test (27) was used to estimate premorbid IQ. Blood samples were taken, and measures of symptoms, functioning, neurocognition, tolerability and safety, and adherence were administered at baseline and 12 weeks as outlined below.

Symptoms and Functioning. Symptomatology was measured using the Positive and Negative Syndrome Scale (PANSS) (28) (coprimary outcome), the Brief Psychiatric Rating Scale Expanded Version (4.0) (29), and the Scale for the Assessment of Negative Symptoms (30). Depression was measured using the Calgary Depression Scale for Schizophrenia (31), mania was measured with the Young Mania Rating Scale (32), and subjective improvement was measured using the Clinical Global Impression scale (33). The Global Assessment of Functioning scale (21) was used to determine global functioning.

Neurocognition. The 11-test neurocognition battery included several tasks from the computerized CogState test battery (34–36) and a range of paper-and-pencil tasks. Six neurocognitive domains were assessed: speed of processing [Trail Making Test–Part A (37) and Simple Reaction Time], attention/vigilance (Identification Test and Monitoring Test), working memory [One-Back Test and Digit Sequencing from the Brief Assessment of Cognition in Schizophrenia (38)], executive function (Trail Making Test–Part B (37) and Mazes subtest from the Neuropsychology Assessment Battery (39)], visual learning and memory [Brief Visuospatial Memory Test–Revised (40) and Associate Learning], and verbal learning and memory [California Verbal Learning Test-II (41) total 1–5 trials]. Each neurocognitive measure at each time point was standardized using the corresponding baseline mean and SD. The signs of change scores were adjusted for each test so that higher scores corresponded to improvement in neurocognition and vice versa. The mean of the corresponding standardized scores was calculated as a summary score for each neurocognitive domain. The composite neurocognitive score (coprimary outcome) was calculated as the average standardized score among the domains assessed. The composite score was coded as missing if any individual neurocognitive items were missing.

Tolerability and Safety. Side effects were assessed at both time points using a semistructured interview for the assessment of side effects of psychotropic medication, the Udvalg for Kliniske Undersogelser (UKU) (42). Each UKU item has a scale of 0 to 3, with 0 = absent/doubtful and 3 = serious. Each UKU item was dichotomized into the categories 0 versus ≥1 to compare the two treatment groups.

Blood and Genotype Analysis. At baseline and follow-up, 30 mL of a fasting blood sample and 10 mL of ethylenediamine tetraacetate blood were collected to measure serum homocysteine, serum folate, red blood cell folate, and serum vitamin B_{12} levels. DNA extracted from whole-blood samples was genotyped for the four variants previously examined in Roffman *et al.* (13) (*FOLH1* 484C>T, rs202676; *MTHFR* 677C>T, rs1801133; *MTR* 1298G>A, rs1805087; and *COMT* 675G>A, rs4680) by the Australian Genome Research Facility using the MassARRAY platform (Sequenom).

Adherence. Adherence to trial medication was measured electronically with the electronic pill caps Medication Event Monitoring System (AARDEX Ltd., Sion, Switzerland). Each time the cap of the tablet container is opened, an electronic record is made indicating that a tablet has been taken. The percentage score over time is measured.

Statistical Analyses

The power analysis was based on a general linear model (GLM) analysis with treatment group as the factor and the baseline values as the covariate. Assuming that the covariate would account for 20% of the variance, the power for detecting a medium effect size is 86% for a sample size of 120 and $\alpha = .05$.

The sample for analysis consisted of all randomized patients with at least one follow-up assessment. The primary analysis was based on the intent-to-treat principle. There were two primary outcomes: 1) change from baseline to week 12 in symptoms defined by the PANSS total score and 2) change from baseline to week 12 in neurocognition defined by the neurocognitive composite score. The two treatment groups were compared on these primary outcomes using GLM analysis with the corresponding baseline score as a covariate. The change in homocysteine, vitamin levels, other symptoms, and neurocognition measures were similarly analyzed to compare treatment groups. The interaction between each of the genetics variables (*MTHFR*, *MTR*, *COMT*, and *FOLH1* genotype) and treatment on the change in the coprimary (PANSS total and neurocognition composite), as well as negative symptom scores (PANSS negative and Scale for the Assessment of Negative Symptoms total) (13), between week 12 and baseline was tested using GLM analysis. Each interaction was tested individually in a separate model, with the corresponding baseline score of each measure as a covariate. Consistent with Roffman *et al.* (13), to maximize sample size, participants who were homozygous for the minor allele were grouped together with heterozygotes. Secondary GLM analysis was also employed to test for the effect of the interaction between baseline homocysteine and treatment, the interaction between sex and treatment, and the interaction between diagnosis and treatment (affective vs. nonaffective) on each of the outcome measures. The analysis was done separately for each interaction. The corresponding baseline score of each measure

was again used as a covariate. In the analysis, baseline homocysteine was dichotomized into normal ≤ 15 (μmoL/L) and high > 15 (μmoL/L) (7). Logistic regression was applied to each UKU item to compare the two treatment groups in terms of the odds of having that particular symptom (i.e., odds of item score ≥ 1); baseline UKU was included as a covariate. Logistic regression analyses were carried out only if the number of participants having that symptom was >5. All statistical tests were two sided, with significance set at $p < .05$. The R statistical package version 3.5.1 (43) and SPSS for Windows version 22 (IBM Corp., Armonk, NY) were used to conduct the analysis.

RESULTS

Sample Characteristics at Baseline

A total of 120 participants were randomized to receive either B vitamins or placebo. Of these participants, 20 dropped out after randomization or baseline assessment with no follow-up assessments and were excluded from the analysis. Of the remaining 100 participants, 52 were randomized to the B-vitamin group and 48 to the placebo group (Figure 1). Baseline demographic, clinical, and symptom characteristics of each treatment group are presented in Table 1. Baseline neurocognition scores and homocysteine, folate, and vitamin B_{12} and B_6 levels are shown in the Supplement. The two groups were comparable on all measures at baseline.

Adherence and Biochemistry

Compliance in taking the trial medication did not differ between the two groups, with the mean Medication Event Monitoring System score over 12 weeks being 65% (SD = 30) for the B-vitamin group and 64% (SD = 32) for the placebo group. There was a significant difference between the two groups in change in homocysteine level, with the vitamin group showing a mean decrease and the placebo group showing little change ($p = .003$). The two groups also significantly differed in terms of the change in red blood cells and serum folate, with the vitamin group showing larger increases than the placebo group ($p < .001$ and $p = .002$, respectively). The vitamin group also showed a higher mean increase in serum B_{12} level, although this was not sufficient to reach significance ($p = .095$) (Table 2).

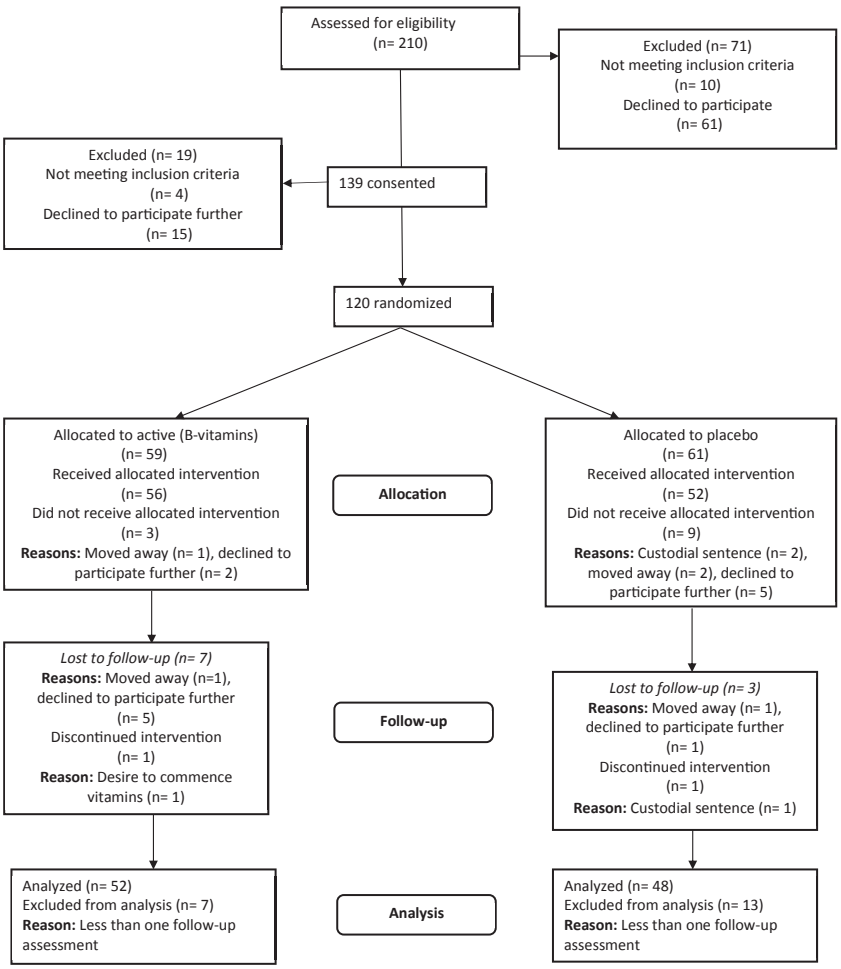

Figure 1. Participant flow.

Table 1. Demographic and Clinical Characteristics of the Two Treatment Groups at Baseline

	Vitamins (n = 52)		Placebo (n = 48)	
	Mean (SD)	n (%)	Mean (SD)	n (%)
Demographic Characteristics				
Age, years	20.2 (3.0)		19.6 (2.4)	
Sex, male		34 (65.4)		34 (70.8)
Australian born		34 (65.4)		37 (77.1)
Currently employed		13 (25.0)		9 (18.8)
Premorbid IQ	103.6 (19.0)		104.4 (11.4)	
Diagnostic Information				
Psychosis onset before 18th birthday		20 (38.3)		18 (37.2)
Schizophrenia		23 (44.2)		26 (54.2)
Schizophreniform disorder		6 (11.5)		6 (12.5)
Schizoaffective disorder		5 (9.6)		3 (6.3)
Bipolar disorder with psychotic features		7 (13.5)		6 (12.5)
Major depression with psychotic features		6 (11.5)		3 (6.3)
Delusional disorder		2 (3.8)		1 (2.1)
Psychotic disorder not otherwise specified		3 (5.8)		3 (6.3)
Symptomatology and Functioning				
PANSS total	57.5 (13.1)		56.7 (13.6)	
PANSS positive	14.5 (4.8)		12.8 (4.4)	
PANSS negative	13.0 (4.4)		14.2 (5.7)	
BPRS total	45.0 (11.3)		42.2 (11.1)	
BPRS psychotic	9.5 (4.0)		8.2 (3.8)	
SANS total	20.1 (14.3)		21.2 (14.6)	
YMRS total	6.5 (6.1)		4.9 (4.6)	
CDSS total[a]	5.6 (5.2)		4.8 (4.5)	
CGI severity of illness	3.5 (1.1)		3.2 (1.1)	
GAF	54.5 (13.7)		54.6 (13.0)	
Prescribed Medication[b]				
Atypical antipsychotic		48 (92.3)		45 (93.8)
Antidepressant		22 (42.3)		20 (41.7)
Mood stabilizer		3 (5.8)		12 (25.0)
Sedative		7 (13.5)		9 (18.8)

BPRS, Brief Psychiatric Rating Scale; CDSS, Calgary Depression Scale for Schizophrenia; CGI, Clinical Global Impression; GAF, Global Assessment of Functioning; PANSS, Positive and Negative Syndrome Scale; SANS, Scale for the Assessment of Negative Symptoms; YMRS, Young Mania Rating Scale.

[a]There was an accidental omission of printing the baseline CDSS in the first batch of assessment packs; hence, n = 41 for the B-vitamin group and n = 38 for the placebo group.

[b]Individuals could be on more than one medication class, so percentages do not add up to 100.

Coprimary Outcomes: Total PANSS and Composite Neurocognition

There was no significant difference between the B-vitamin and placebo groups in change in the coprimary outcomes of PANSS total and neurocognition composite over 12 weeks (p = .749 and p = .785, respectively) (Tables 3 and 4).

Table 2. Mean Change Scores (Week 12 Minus Baseline) for Blood Measures

	Vitamins		Placebo			
	Mean	SD	Mean	SD	p Value[a]	Effect Size
Homocysteine	−2.4	4.2	−0.3	4.4	.003	−0.65
Red Blood Cell Folate	276.0	351.7	50.9	251.1	<.001	0.88
Serum Folate	13.7	18.9	5.3	14.1	.002	0.77
Serum Vitamin B_{12}	107.3	130.7	42.5	122.8	.095	0.37

[a]p Value comparing the two groups using general linear model analysis with baseline score as a covariate.

Secondary Psychopathology and Neurocognitive Outcomes

The change in secondary psychopathology measures and global functioning over 12 weeks did not significantly differ between the two treatment groups (Table 3). With respect to neurocognitive domains, a significant group difference was observed in attention/vigilance (p = .024, effect size = 0.49), where overall the B-vitamin group remained stable and the placebo group declined over the 12 weeks (Table 4). Examination of the individual neurocognitive tests revealed that change in performance on the Identification Test was significantly different between groups, with stability in the vitamin group and decline in the placebo group overall (p = .027, effect size = 0.48).

Table 3. Change Scores (Week 12 Minus Baseline) in Psychopathology and Functioning

Symptom Domain	Group	Mean	SD	n	p Value[a]	Effect Size
PANSS Total	Placebo	−5.41	14.13	48	.749	0.07
	Vitamin	−4.76	13.98	47		
PANSS Positive	Placebo	−1.48	4.26	48	.552	0.12
	Vitamin	−1.98	6.40	47		
PANSS Negative	Placebo	−0.79	4.89	48	.999	0.00
	Vitamin	−0.39	3.85	47		
BPRS Total	Placebo	−4.19	12.08	48	.988	0.00
	Vitamin	−5.66	12.35	47		
BPRS Psychotic	Placebo	−1.06	3.79	48	.541	0.13
	Vitamin	−1.32	4.72	47		
SANS Total	Placebo	−2.09	12.15	47	.748	−0.07
	Vitamin	−2.68	13.12	47		
YMRS Total	Placebo	0.33	5.84	46	.354	−0.20
	Vitamin	−1.98	6.85	46		
CDSS Total	Placebo	−1.62	4.13	37	.801	0.06
	Vitamin	−1.87	4.94	38		
CGI Severity of Illness	Placebo	−0.24	1.19	45	.310	−0.22
	Vitamin	−0.63	1.16	43		
GAF	Placebo	6.02	13.94	48	.333	0.20
	Vitamin	8.96	13.90	46		

BPRS, Brief Psychiatric Rating Scale; CDSS, Calgary Depression Scale for Schizophrenia; CGI, Clinical Global Impression; GAF, Global Assessment of Functioning; PANSS, Positive and Negative Syndrome Scale; SANS, Scale for the Assessment of Negative Symptoms; YMRS, Young Mania Rating Scale.

[a]p Value comparing the two groups using general linear model analysis with baseline score as a covariate.

Table 4. Change Scores (Week 12 Minus Baseline) of Standardized Neurocognition Measures

	Group	Mean	SD	*n*	*p* Value[a]	Effect Size
Neurocognitive Composite	Placebo	0.20	0.34	40	.785	−0.06
	Vitamin	0.17	0.29	36		
Domains						
Speed of processing	Placebo	0.13	0.68	44	.751	0.07
	Vitamin	0.16	0.57	43		
Attention/vigilance	Placebo	−0.23	0.54	45	.024	0.49
	Vitamin	0.05	0.60	42		
Working memory	Placebo	0.34	0.82	41	.101	−0.38
	Vitamin	−0.08	0.70	38		
Executive functioning	Placebo	0.45	0.56	41	.961	−0.01
	Vitamin	0.30	0.54	42		
Verbal learning and memory	Placebo	0.18	0.66	42	.951	0.12
	Vitamin	0.17	0.64	41		
Visual learning and memory	Placebo	0.28	0.69	44	.585	0.01
	Vitamin	0.36	0.79	44		
Neurocognitive Tests						
TMT–Part A	Placebo	0.51	0.83	45	.362	0.19
	Vitamin	0.58	0.90	45		
Simple Reaction Time	Placebo	−0.23	1.02	45	.905	0.03
	Vitamin	−0.19	0.81	43		
Identification Test	Placebo	−0.29	0.71	46	.027	0.48
	Vitamin	0.02	0.71	43		
Monitoring Test	Placebo	−0.16	0.80	46	.215	0.27
	Vitamin	0.08	0.95	42		
One-Back Test	Placebo	0.35	1.49	46	.445	−0.17
	Vitamin	−0.20	1.28	43		
Digit Sequencing	Placebo	0.22	0.79	41	.748	0.07
	Vitamin	0.20	0.61	40		
Mazes	Placebo	0.37	0.62	42	.880	0.03
	Vitamin	0.31	0.66	42		
TMT–Part B	Placebo	0.51	0.78	44	.936	−0.02
	Vitamin	0.36	0.79	45		
BVMT	Placebo	−0.01	0.58	42	.464	0.16
	Vitamin	0.07	0.79	43		
Associate Learning	Placebo	0.37	1.03	45	.980	0.00
	Vitamin	0.36	0.96	43		
CVLT	Placebo	0.28	0.69	44	.585	0.12
	Vitamin	0.36	0.79	44		

BVMT, Brief Visuospatial Memory Test; CVLT, California Verbal Learning Test; TMT, Trail Making Test.

[a]*p* Value comparing the two groups using general linear model analysis with baseline score as a covariate.

Effect of Baseline Homocysteine Level

Of the participants, 14% had elevated homocysteine levels (>15 μmoL/L) at baseline. Analysis of whether baseline homocysteine levels (≤15 vs. >15 μmoL/L) interacted with treatment effects showed that a homocysteine by treatment interaction was significant for one outcome measure, the Identification Test ($p = .025$). There was no significant difference between treatments in change in Identification Test performance in the normal homocysteine level group (placebo mean = −0.24, SD = 0.72, vitamins mean = −0.07, SD = 0.71, $p = .234$, effect size = 0.27). In the elevated homocysteine group, the two groups were significantly different, with the B-vitamin group showing a mean improvement and the placebo group showing a mean drop in Identification Test performance over 12 weeks (placebo mean = −0.55, SD = 0.63, vitamins mean = 0.51, SD = 0.55, $p = .003$, effect size = 1.61) (Figure 2).

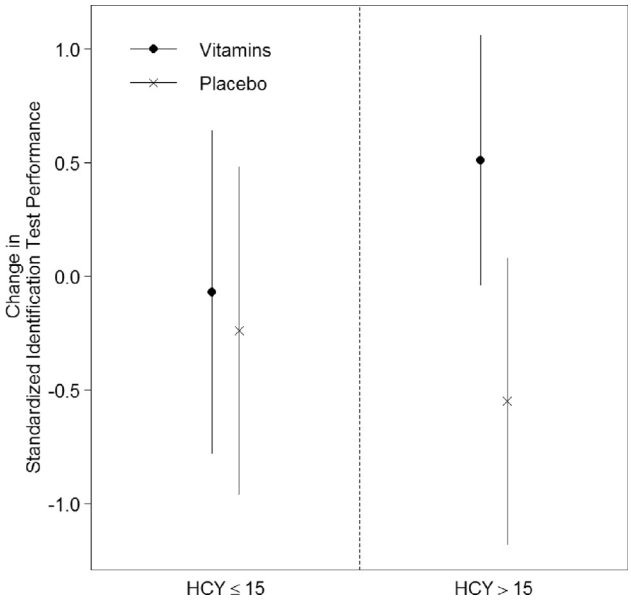

Figure 2. Plot of mean ± 1 SD of change in standardized Identification Test (week 12 minus baseline) for the vitamin and placebo groups within each of the two baseline homocysteine (HCY) groups.

Effect of Genetic Polymorphisms

There were no significant interactions between the four genetic variations and treatment condition in relation to change in PANSS total, cognition composite, PANSS negative, or Scale for the Assessment of Negative Symptoms total over the 12 weeks (all *p*s > .05).

Effect of Sex

The sex by treatment interaction was found to be significant in only two cognition outcome measures: speed of processing ($p = .029$) and attention/vigilance ($p = .030$). Post hoc pairwise *t* tests comparing the two treatment groups within each sex showed that within male participants, there was no significant difference between the two treatment groups on either measure ($p > .30$ for both measures). Within female participants, the two groups showed a significant difference on both measures ($p = .049$, effect size = 0.74 and $p = .002$, effect size = 1.20, for speed of processing and attention/vigilance, respectively), with the B-vitamin group showing a mean improvement but the placebo group showing a mean decline on both measures.

Effect of Diagnosis

The diagnosis (affective vs. nonaffective) by treatment interaction was found to be significant for two outcome measures:

Monitoring Test (p = .022) and attention/vigilance (p = .011). Post hoc pairwise t tests comparing the two treatment groups within each diagnostic group showed that within the non-affective group, there was no significant difference between the two treatment groups on either measure ($p > .60$ for both measures). Within the affective group, the two groups showed a significant difference on both measures (p = .013, effect size = 1.02 and p = .001, effect size = 1.39, for Monitoring Test and attention/vigilance, respectively), with the B-vitamin group showing a mean improvement but the placebo group showing a mean decline on both measures.

Safety and Tolerability

There were low rates of side effects in the overall sample, and there were no significant group differences on any UKU items (data available from authors on request).

DISCUSSION

This is the first study to examine the efficacy of folate and vitamin B_{12} and B_6 supplementation in an FEP population and to examine the potential interaction effects associated with baseline homocysteine, genetic variation, sex, and diagnosis on effectiveness. The B-vitamin supplement resulted in significantly lowered homocysteine (and increased folate) blood levels. However, B vitamins resulted in no significant benefit over placebo with respect to total symptoms or composite neurocognition (coprimary outcomes) or in most of the secondary outcomes over 12 weeks. One exception was for attention/vigilance, in which the mean performance of the placebo group declined over 12 weeks, whereas performance in the B-vitamin group remained stable. Attention/vigilance was the most sensitive domain to the neurocognitive effects of B vitamins, with large improvements in this domain in response to vitamins being more likely in female participants, participants with affective psychosis, and the subgroup of participants who had elevated baseline homocysteine levels. B vitamins were well tolerated and had minimal side effects, consistent with previous research (13).

Our finding that adjunctive B vitamins were ineffective for improving psychiatric symptoms is in contrast to previous trials (7,13,16,17). Notably, the participants in previous studies had long-term schizophrenia with much higher baseline levels of symptomatology than the participants in the current study (7,13,17). Heterogeneity of psychotic diagnosis and participants' symptom levels in the current study may have limited the range for an overall effect to be shown. Furthermore, baseline blood levels of folate and vitamin B_{12} on average were lower and baseline levels of homocysteine were much higher in previous studies compared with the current study (13,16), where homocysteine was on average in the normal range. Indeed, the improvement on the Identification Test in the B-vitamin subgroup of patients with FEP with elevated homocysteine suggests that individuals who have abnormal homocysteine or blood vitamin levels may be the most responsive to adjuvant vitamin treatment, strongly supporting a precision medicine or biomarker-guided treatment approach (44).

Furthermore, recent RCTs in other psychiatric conditions (i.e., major depression) have demonstrated that significant benefits of vitamin supplementation are achieved at higher doses than used in our study. For instance, 15 mg daily of L-methylfolate (a more bioavailable version of folic acid) significantly reduced symptoms of treatment-resistant major depression, whereas 7.5 mg daily did not (45). Symptomatic benefits from L-methylfolate may also occur from the anti-inflammatory (rather than homocysteine-reducing) effects, with the greatest reductions in depression being observed in patients with elevated inflammatory cytokines (46). A recent study in long-term schizophrenia also found significant reductions in negative symptoms, along with improvements in white matter, from 15 mg daily of L-methylfolate after just 12 weeks (17). Thus, the generally null results of this trial could suggest that higher doses of more bioactive versions of folate supplementation are required to produce noticeable benefits for symptomatology within 12 weeks in FEP.

Secondary analysis showed that B vitamins may have some neuroprotective properties, with evidence showing that they prevented a decline in attention/vigilance over 12 weeks. Previous research suggests that a dose–response relationship exists between increases in homocysteine and risk of schizophrenia, providing a rationale for using homocysteine levels as a biological parameter for intervention studies (1). Our findings partially support this, with high homocysteine levels being associated with better neurocognitive outcomes following vitamin treatment. Hyperhomocysteinemia has been proposed to cause oxidative stress in schizophrenia, which may have negative effects on the brain and neurocognition (1). Support for this comes from trials of older people with mild cognitive impairment. In one study, patients with mild cognitive impairment showed that 2 months of folic acid increased attention, and this effect was strongest in those with low baseline plasma folate (47). A study of 24 months of B-vitamin supplementation in patients with mild cognitive impairment showed that slower brain atrophy owing to treatment was correlated with baseline plasma homocysteine levels (48). Finally, a large study of healthy older adults showed that 3 years of folic acid supplementation resulted in better memory and processing speed compared with placebo, with the greatest benefits being observed in those with elevated baseline homocysteine (49). Together, these findings suggest that a simple blood test showing elevated homocysteine at entry to treatment for FEP may indicate that vitamin supplementation at an adequate dose is warranted to prevent neurocognitive decline. Future trials that select participants with high homocysteine levels are now needed to confirm these findings and investigate generalization to other clinical and brain measures.

For aging-related cognitive decline, the beneficial neurological effects of B-vitamin supplementation are dependent on polyunsaturated fatty acid levels, with improvements in brain structure and function from B-vitamin supplementation occurring only in individuals with high omega 3 (50,51). Omega 3 levels are often low in FEP, and supplementation has been shown to improve neurological markers of brain health (52), introducing the possibility of using B vitamins alongside omega 3 supplements for synergistic effects on neurological and psychological outcomes. Given the high tolerability and low side-effect profiles of nutritional supplements, future research could explore using targeted multinutrient interventions for synergistic action in FEP.

Although previous evidence suggested that male patients may preferentially benefit from vitamin supplementation (53), secondary analysis of the effects according to sex found that B vitamins had no significant effect on symptoms or neurocognition in male patients with FEP. Our sample comprised a larger proportion of female patients than previous studies of long-term schizophrenia (7,17). Unexpectedly, we found that the vitamin-treated female patients significantly improved in the neurocognitive domains of speed of processing and attention/vigilance. Supplementary analysis showed that the effect in female patients was not due to a higher compliance with the trial supplement (data not shown). It is unclear why female patients benefited more than male patients; this novel finding should be considered tentative and requires replication.

Finally, variants in the genes involved in the folate metabolic pathway did not interact with the effect of B vitamins on psychopathology or neurocognition in this FEP sample. While there is evidence suggesting a possible link between genetic polymorphisms (e.g., in *MTHFR*), elevated homocysteine, and schizophrenia, this link has not yet been definitively established (9). Only two previous studies in schizophrenia have examined the role of genetic polymorphisms in response to vitamin supplementation, and findings were mixed. One study showed that negative symptom improvement was seen in individuals homozygous for the 484T allele of *FOLH1* (13), whereas another showed that total and general symptom improvement was influenced by the *MTR* 2756A4G variant (17).

The current study had some limitations. All patients were prescribed antipsychotic medication (which was not standardized) and had lower levels of psychotic symptomatology than those in previous studies, which may influence the outcome. We did not measure or examine the effects of obesity, smoking, or excessive caffeine consumption, although previous research in FEP has shown that caffeine and smoking had no effect on homocysteine levels (9). We did not conduct adjustment for multiple testing, which may be perceived as a limitation. However, there is no agreement among statisticians as to whether adjustments should or should not be done (54). Our strategy was to report all tests and results and regard the findings as tentative (54,55). Finally, the study may have been underpowered to detect influences of genetic variation on response to vitamin treatment.

In conclusion, this trial provided no evidence to suggest an overall benefit of adjuvant folate or vitamin B_{12} or B_6 on psychopathology or general neurocognition in FEP. However, secondary analyses showed that B vitamins may be beneficial for attention/vigilance, particularly in individuals with elevated homocysteine, individuals with affective psychosis, and female individuals. Further research will be necessary to confirm the factors that moderate effects of homocysteine-reducing treatments in FEP. This is the premise of biomarker-stratified and personalized medicine, with the next generation of nutrition intervention trials taking into account baseline nutritional status (56). Future studies should examine the effects of B vitamins in patients with FEP with elevated homocysteine or certain illness features and whether significant benefits are observed from higher doses of more bioavailable B-vitamin supplements or from combining these with other nutrients.

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ClinicalTrials.gov: Efficacy of Treating First Episode Psychosis With Folic Acid, B12 and B6 in Addition to Antipsychotic Medication; https://clinicaltrials.gov/ct2/show/NCT00202280; NCT00202280.

ARTICLE INFORMATION

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