Vitamins B_{12}, B_6, and Folic Acid for Onset of Depressive Symptoms in Older Men: Results From a 2-Year Placebo-Controlled Randomized Trial

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Objective: To examine whether use of vitamins B_{12}, B_6, and folate was associated with reduced severity of depressive symptoms and 2-year incidence of clinically significant depression.

Method: The investigators recruited 299 men aged 75 years and older free of clinically significant depression (Beck Depression Inventory [BDI] score < 18). They were randomly assigned to treatment with 400 μg B_{12} + 2 mg folic acid + 25 mg B_6 per day (N = 150) or placebo (N = 149). The BDI was the primary outcome measure of the study. Follow-up assessments took place 6, 12, 18, and 24 months after baseline. Analyses were intention-to-treat. The study was conducted from June 2001 to June 2004.

Results: 118 and 123 men treated with vitamins and placebo, respectively, completed this 2-year trial (19.4% dropout rate). Analysis of variance for repeated measures showed that there was no difference between the groups ($F = 0.76$, $df = 1$, $p = .384$) nor was there a significant change of BDI scores over time ($F = 1.26$, $df = 4$, $p = .284$). Cox regression revealed that participants treated with vitamins were 24% more likely to remain free of depression during the trial, although the difference between groups was not significant (95% CI = 0.68 to 2.28). At the end of the study, 84.3% of men treated with vitamins and 79.1% of those treated with placebo remained free of clinically significant depressive symptoms. The number of people needed to treat to show benefit was 21.

Conclusion: The results of this study showed that treatment with B_{12}, folic acid, and B_6 is no better than placebo at reducing the severity of depressive symptoms or the incidence of clinically significant depression over a period of 2 years in older men.

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Depression is a leading cause of disability worldwide, affecting 2% to 5% of the adult population.[1] The causal pathway that leads to the development of depression is likely to be varied and complex, but preliminary evidence suggests that deficiencies of B vitamins contribute to the onset and maintenance of clinically significant depressive symptoms.[2–4] Folate and vitamins B_6 and B_{12} are important cofactors in the metabolism of methionine and homocysteine. Low folate is associated with high total plasma homocysteine (tHcy), which in turn is associated with increased risk of cerebrovascular disease. Cerebrovascular disease is an important risk factor for depression.[5] Methionine is the immediate precursor of S-adenosylmethionine (SAM), the methyl donor of numerous methylation reactions in the brain, many of which are directly involved in the synthesis and metabolism of monoamines such as dopamine, norepinephrine, and serotonin.[6] These neurotransmitters are thought to play an important role in the pathogenesis of depression.[7]

Clinically, several cross-sectional studies have shown that depressed patients in contact with mental health services have lower concentrations of B vitamins in the serum than nondepressed patients or controls without

a mental health disorder.[3,8–14] Some community-based studies have also observed low concentration of B vitamins among participants meeting criteria for depression, although findings across studies are not always consistent. The Rotterdam Study[15] screened a community-representative sample of 3884 older adults for depressive symptoms, of whom 112 were diagnosed with a depressive disorder according to *Diagnostic and Statistical Manual of Mental Disorders,* Fourth Edition (DSM-IV) criteria. The odds of depression among people with vitamin B_{12} deficiency were 1.69 (95% CI = 1.10 to 2.56) after adjustment for age and gender. Likewise, depression was significantly more likely in people with high tHcy (OR = 2.07, 95% CI = 1.11 to 3.86) but not folate deficiency (OR = 1.52, 95% CI = 0.85 to 2.71).[15] Another large cross-sectional survey of 5948 adults and older adults found that subjects with high tHcy (> 15.0 μmol/L) were twice as likely (95% CI = 1.17 to 3.41) to meet the study criterion for depression (Hospital Anxiety and Depression Scale, depression subscore ≥ 8) as participants with tHcy < 15 μmol/L.[16] Plasma folate was inversely associated with depression scores in women aged 46 to 49 years, but no obvious association was found with the plasma concentration of vitamin B_{12}.[16] The SALSA study,[17] which investigated a community-representative cross-sectional sample of 627 men and 883 women, found that depression (Center for Epidemiologic Studies Depression Scale score ≥ 16) was twice as likely (95% CI = 1.38 to 3.02) to occur in women in the lowest tertile of folate concentration, although no such association was observed among men. Similarly, a cross-sectional analysis of a subsample of 412 people aged 60 to 64 years derived from the Personality and Total Health Study Australian cohort found that the lowest quartile of folate concentration was associated with increased number of depressive symptoms, as assessed by the Primary Care Evaluation of Mental Disorders (PRIME-MD) Patient Health Questionnaire.[18] Other studies found that depression is associated with high tHcy in men[19,20] and women,[21] but not necessarily with low folate, B_6, or B_{12} concentrations.[15,16,22]

As far as we are aware, only 1 study has prospectively investigated the association between folate and depression. A total of 2313 community-dwelling men aged 42 to 60 years were recruited as part of the Kuopio Ischaemic Heart Disease Study between 1984 and 1989.[23] As part of their assessment, participants rated a detailed dietary questionnaire from which estimates of folate intake were derived. Using administrative data linkage, the investigators followed this cohort until the end of 2000, at which point 53 participants had a recorded new diagnosis of depressive disorder. Subjects who reported folate intake below the median value of the sample were 2.53 times as likely (95% CI = 1.17 to 5.48) to receive the diagnosis of depression as men in the higher half of folate intake. Dietary intake of vitamin B_{12} showed no obvious association with incident depression.[23]

Six clinical trials reported the results of folate supplementation on the mood of people with depression. Table 1 summarizes their main characteristics and findings. Together, these studies evaluated the effect of some form of B-vitamin supplementation in a heterogeneous group of 364 patients with clinically significant depressive symptoms. All these studies were confounded by antidepressant treatment. The results of a recent meta-analysis that included 2 of these studies[25,28] suggested that folate supplementation might have a role to play in the treatment of depression,[30] although the number of patients studied to date is very small and reported benefits associated with B-vitamin use are often based on post hoc comparisons of subgroups of patients.

We designed the present study to determine whether treatment with B vitamins for 2 years reduces the onset of clinically significant depressive symptoms in older men.

METHOD

Participants

We recruited a random sample of 299 men aged 75 years or older from a large (N = 12,203) population-based study of abdominal aortic aneurysm screening.[31] These men were originally recruited for a placebo-controlled trial addressing the effect of vitamins B_{12}, B_6, and folate on cognitive decline and depression.[32] The men were identified from an electronic copy of the electoral roll (enrollment to vote being compulsory for Australian adults) in Perth, Western Australia. All subjects either were being treated for, or had a history of, hypertension. Participants were excluded if they had a Beck Depression Inventory (BDI)[33] score of 18 or higher and significant cognitive impairment as evidenced by a Mini-Mental State Examination (MMSE)[34] score of less than 24 points. We excluded from the trial subjects who had an illness deemed likely to cause severe disability or death within 12 months (for example, metastatic cancer, Parkinson's disease, or history of stroke), who were living in residential care facilities, or who were non–English speaking, and those who were already taking vitamin B supplements. All participants gave informed consent. The Human Research Ethics Committee of the University of Western Australia approved the protocol for the study, which carries number 12605000045617 from the Australian New Zealand Clinical Trials Registry (www.anzctr.org.au). The study was conducted from June 2001 to June 2004.

Randomization

Participants were given consecutive numbers and allocated to active versus placebo arms on the basis of computer-generated random permuted blocks. Blocks

Table 1. Characteristics of Clinical Trials Investigating the Outcome of Depression Treated With Various Forms of Folate

Study	Study Design	Participants	Intervention	Outcome Measures	Comments
Coppen et al, 1986[24]	Double-blind, placebo-controlled trial (allocation concealment unclear)	75 patients with unipolar and bipolar disorder	200 µg/d of folic acid or placebo for 12 mo in addition to lithium	Reduction in BDI score	Subgroup analysis of patients with unipolar depression treated with folic acid showed greater reduction in BDI scores; no adjustment was made for multiple comparisons
Godfrey et al, 1990[25]	Double-blind, placebo-controlled randomized trial (allocation concealment unclear)	24 patients with major depression according to DSM-III	15 mg/d of MTHF or placebo in addition to standard antidepressant treatment for 6 mo	HAM-D score and Clinical Outcome Scale (clinical impression regarding clinical and social functioning)	Significant decline in clinical outcome scores (but not HAM-D) in the group treated with MTHF at 3 and 6 mo
Guaraldi et al, 1993[26]	Open-label trial	20 older adults with major depression according to DSM-III-R	50 mg/d of MTHF for 6 wk; no other psychotropic medications used	HAM-D score	13/16 patients who completed the trial had a decline of 50% or more on the scores of the HAM-D
Passeri et al, 1993[27]	Double-blind, controlled trial (allocation concealment unclear)	96 patients with cognitive impairment (MMSE score < 24) and depression (HAM-D score > 17)	50 mg/d of MTHF or 100 mg/d of trazodone for 8 wk	HAM-D score	Significant decline in HAM-D scores at 4 and 8 wk in both treatment groups
Coppen and Bailey, 2000[28]	Double-blind, placebo-controlled randomized trial (allocation concealment unclear)	127 patients with a major depressive episode (DSM-III-R)	500 µg/d of folic acid or placebo in combination with fluoxetine for 10 wk	HAM-D score	Subgroup analysis showed that only women treated with folic acid gained extra benefit from antidepressant treatment; only people completing 6 wk of treatment were included in the analysis
Alpert et al, 2002[29]	Open-label trial	22 patients with major depressive disorder (DSM-IV)	15 mg/d for 2 wk and 30 mg/d for 6 wk of folinic acid in combination with fluoxetine (N = 12), sertraline (N = 6), paroxetine (N = 3), or venlafaxine (N = 1)	HAM-D score	Subgroup analysis showed that only 5/16 patients had a decline in HAM-D scores of 50% or more

Abbreviations: BDI = Beck Depression Inventory, DSM = *Diagnostic and Statistical Manual of Mental Disorders*, HAM-D = Hamilton Rating Scale for Depression, MMSE = Mini-Mental State Examination, MTHF = methyltetrahydrofolate.

consisted of 8 subjects (4 subjects allocated to each group) so as to minimize the risk of having unbalanced entry into each arm of the study during the period of recruitment. An external and independent academic controlled the randomization procedures of the trial.

Interventions and Blinding

Vitamins and placebo were administered in the form of oral capsules that had the same shape, size, color, texture, and taste. The active medication consisted of 400 µg B_{12}, 2 mg folic acid, and 25 mg B_6. These doses have been shown to be effective in lowering homocysteine levels.[32,35] All men were advised to consume 1 capsule every morning for 2 years. Participants and investigators were blinded to the group membership of men in the trial until the last follow-up assessment was completed. There were no breaches of protocol.

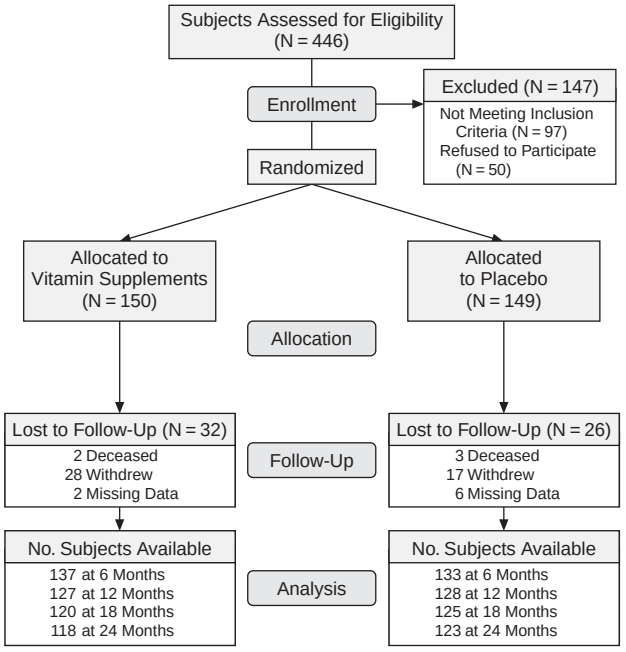
Assessment Procedures

Participants were assessed at baseline and after 6, 12, 18, and 24 months from randomization. We collected information on age (in years), education (age at which subject left school), and alcohol use (standard drinks consumed per day in a typical week). For the purposes of this study, men were considered to be consuming alcohol at harmful or hazardous levels if they reported drinking more than 4 standard drinks per day at least 5 days per week, or more than 6 standard drinks on any 1 day. We also used the standardized form of the MMSE as a general measure of cognitive function.[36]

Outcomes of Interest

The BDI[33] was the primary outcome measure of this study. This widely used and valid self-rating scale consists of 21 questions assessing various depressive symptoms, each yielding a rating between 0 and 3. Possible total score ranges from 0 to 63, with higher scores indicating greater severity of symptoms. Beck and colleagues[33] established that a total score of 0 to 9 is associated with no or minimal depression, 10 to 18 with mild to moderate depression, 19 to 29 with moderate to severe depression, and 30 to 63 with severe depression.

Figure 1. Flow of Participants in the Trial From Eligibility Assessment to the End of the 24-Month Intervention



Endpoints of interest in this study were (1) increase of BDI scores during the 2-year follow-up period and (2) total BDI score greater than 9 (suggestive of the presence of at least mild depressive symptoms) at any follow-up assessment.

Assay Techniques

Subjects had fasting blood samples taken between the hours of 8:30 and 11:00 a.m. Serum B_{12} and red cell folate were measured by standard competitive assays using the Abbott AxSYM analyzer (Abbott Laboratories, Abbott Park, Ill.). Total plasma homocysteine levels were determined by reverse-phase high-performance liquid chromatography after treatment with tributylphosphine, deproteinization, and fluorogenic derivatization using the method of Araki and Sako.[37]

Analysis of Data

We used SPSS version 10.0 (SPSS Inc., Chicago, Ill.) to manage and analyze the data. Descriptive statistics and graphic methods were used to investigate the distribution of the data. We used Student t test to compare the differences between the groups for normally distributed data and the Mann-Whitney test for ordinal data (z statistic value). The frequency distribution of categorical variables was evaluated with the Pearson χ^2. The odds ratio was also calculated from 2×2 tables. We investigated the outcomes of interest in 3 different ways: (1) analysis of variance for repeated measures of the difference between BDI scores at 6, 12, 18, and 24 months compared with baseline, (2) Cox proportional hazard to determine the proportion of participants who became depressed during the 24-month intervention period (excluding those who had a BDI score ≥ 10 at baseline), and (3) proportion of men who were mildly depressed at baseline and remitted during the 24-month intervention period. Analyses were based on intention-to-treat using the method of last observation carried forward, as well as on completers. We also investigated the correlation between changes in the concentration of B vitamins and tHcy and changes in BDI scores using Pearson product moment correlation coefficient. The number needed to treat was calculated as the reciprocal of the absolute risk reduction associated with treatment. Alpha was set at 5%, and all probability values reported are 2-tailed. Figure 1 shows the flow of participants from the eligibility assessment to the end of the 24-month intervention.

RESULTS

Men were randomly allocated to the placebo (N = 149) and vitamin (N = 150) groups. Table 2 summarizes the baseline characteristics of participants. The groups were well matched on all variables except age—men in the vitamin group were older than placebo controls, but the difference between the groups was less than 1 year.

Figure 2 shows the changes in BDI scores relative to baseline among men taking vitamins and placebo (intention-to-treat). Analysis of variance for repeated measures showed that there was no difference between the groups ($F = 0.76$, $df = 1$, $p = .384$), nor was there a significant change of scores over time ($F = 1.26$, $df = 4$, $p = .284$).

We also examined the proportion of people who were free of clinically significant depressive symptoms at baseline (i.e., BDI < 10) but became depressed during the trial (i.e., BDI ≥ 10). Figure 3 illustrates the relative proportion of men who were free of depression at baseline and remained free of depression throughout the trial (N = 138 in each group; intention-to-treat). Cox regression analysis showed that participants treated with vitamins were 24% more likely (hazard ratio [HR] = 1.24, adjusted for age at baseline) to remain free of depression during the trial, although the difference between groups was not significant (95% CI = 0.68 to 2.28). At the end of the study, 84.3% of men treated with vitamins and 79.1% of those treated with placebo remained free of clinically significant depressive symptoms. The number of people needed to treat to show benefit was 21.

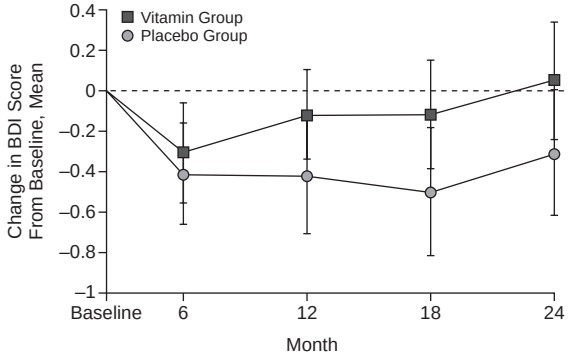
Post hoc analysis showed that the study had only 16% power to declare a difference of this magnitude between the groups significant. (We would need to treat 905 people with vitamins and 905 with placebo to show a 5%

Table 2. Characteristics of Men Randomly Allocated to the Placebo and Vitamin Groups at the Baseline Assessment

Characteristic	Placebo (N = 149)	Vitamins (N = 150)	Statistic[a]	p Value
Age, mean (SD), y	78.7 (2.7)	79.3 (2.7)	t = 1.97	.050
Education: age left school, mean (SD)	15.1 (1.7)	15.0 (1.7)	t = 0.10	.924
Harmful or hazardous alcohol use, N (%)	20 (13.4)	13 (8.7)	$\chi^2 = 1.72$	.189
BDI score, mean (SD)	6.3 (3.9)	6.1 (4.4)	z = –0.82	.415
MMSE score, mean (SD)	27.6 (1.9)	27.5 (1.8)	z = –0.99	.325

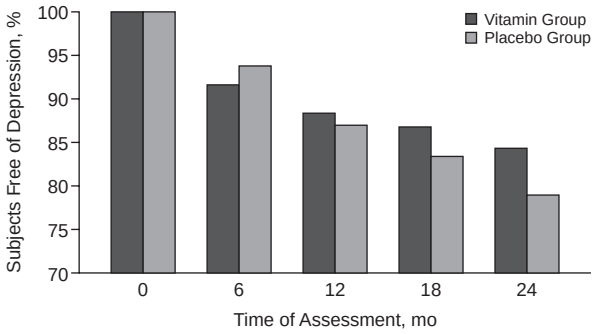
[a]The number of degrees of freedom for all t tests is 297, and for the χ^2 tests, df = 1.
Abbreviations: BDI = Beck Depression Inventory, MMSE = Mini-Mental State Examination.

Figure 2. Changes in Beck Depression Inventory (BDI) Scores Relative to Baseline Among Older Men After 6, 12, 18, and 24 Months of Treatment With B Vitamins or Placebo[a]



[a]The circles and squares show the mean BDI difference from baseline with the standard error bars of the mean at each time point.

Figure 3. Proportion of Older Men Who Were Free of Clinically Significant Depressive Symptoms at Baseline and Remained So Throughout the Trial



difference in the proportions of people free of depression with 80% power.)

Twenty-three men had BDI scores between 10 and 17, inclusive, at baseline. Twelve were randomly allocated to treatment with vitamins and 11 to placebo. Analysis of variance for repeated measures did not show any difference between the groups during the 24 months of treatment (F = 0.25, df = 1, p = .626). After 24 months, 6 of 12 men treated with vitamins were still depressed compared with 8 of 11 in the placebo group ($\chi^2 = 1.24$, df = 1, p = .265).

Thirty-two and 26 men in the vitamin and control groups, respectively, either dropped out or did not complete the BDI at the end of 2 years (Figure 1; $\chi^2 = 0.72$, p = .396). Twenty-four month compliance with treatment, according to pill count, was greater than 50% for 123 of 150 men (82.0%) treated with vitamins and for 125 of 149 (83.9%) of those treated with placebo ($\chi^2 = 0.19$, df = 1, p = .664). Subjects who were depressed at least once during the trial (N = 98/299) were as likely to be compliant (84.7% [83/98]) as men who were never depressed (82.1% [165/201]) ($\chi^2 = 0.32$, df = 1, p = .574).

Analysis of variance for repeated measures limited to those who completed the trial showed no difference between the 2 treatment groups in relation to changes in BDI scores over time (F = 0.02, df = 1, p = .898). Cox regression revealed that treatment with vitamins was not less likely to be associated with depression during the trial (HR = 1.12, 95% CI = 0.56 to 2.22). Similarly, when only patients who were depressed at baseline were included in an analysis of variance for repeated measures of BDI scores over 24 months, no difference between men treated with vitamins or placebo was observed (F = 0.04, df = 1, p = .864).

Finally, we investigated the correlation between changes in BDI scores and changes in the concentration of vitamin B_{12} (r = 0.08, p = .215), red cell folate (r = 0.07, p = .318), and tHcy (r = –0.04, p = .549) for those who had completed the initial and final assessments of the study. The correlations were all very poor. There was no difference between men with and without depression in the mean concentrations of B_{12} (379.2 pmol/L, SD = 204.3 pmol/L vs. 421.2 pmol/L, SD = 214.0 pmol/L; t = –1.09, p = .277), red cell folate (1383.4 nmol/L, SD = 445.4 nmol/L vs. 1372.5 nmol/L, SD = 499.9 nmol/L; t = 0.12, p = .904), or tHcy (12.7 μmol/L, SD = 3.1 μmol/L vs. 12.6 μmol/L, SD = 4.2 μmol/L; t = 0.18, p = .857) at the 24 month assessment. Changes over time in the concentration of tHcy, folate, and B_{12} have been reported elsewhere.[32]

Forty-three men (28.7%) and 32 men (21.5%) randomly allocated to treatment with vitamins and placebo, respectively, had plasma tHcy ≥ 15 μmol/L at baseline ($\chi^2 = 2.26$, df = 1, p = .133), compared with 9 of 113 men (8.0%) and 43 of 122 men (35.2%) after 24 months of treatment ($\chi^2 = 26.63$, df = 1, p < .001; no plasma available for 6 and 1 subjects treated with vitamins and placebo, respectively). At the end of the trial, subjects treated

with B vitamins were 6.3 times less likely than placebo controls to have high plasma tHcy (95% CI = 2.8 to 15.4).

DISCUSSION

The results of this 24-month randomized trial showed that treatment with vitamins B_{12}, B_6, and folic acid was not associated with a significant change in the mood of older men. We investigated the association between vitamin use and depression in 3 different ways, none of which showed an advantage of B vitamins compared with placebo over 24 months: change in BDI scores, incidence of clinically significant depressive symptoms, and remission of depression.

Before discussing the implications of our results and how they compare with previously published reports, we should consider the methodological aspects of this trial. The study was limited to men aged 75 years or older with a prior history of hypertension. The selection of this particular group of participants aimed to increase the number of people who would potentially benefit most from treatment with vitamins. Our previous results demonstrated that treatment with B vitamins markedly reduces tHcy concentration,[32] but this reduction has no obvious effect on the mood of older men. In addition, the design of our study excluded men with severe depression at the time of recruitment, as we did not wish to withhold best available treatment from participants. Family physicians were informed about depression scores so that they could adjust the management of their patients accordingly, but men who became depressed during the trial were not excluded. As a consequence, we cannot entirely dismiss the possibility that B vitamins could be helpful in the treatment of people with severe depressive symptoms, although 21 people would need to be treated with B vitamins for 1 to benefit (i.e., high number needed to treat). We concede, however, that the study might have been underpowered to detect an effect of the intervention on depression outcomes, particularly because we could not take into account use of antidepressants during the trial. We also acknowledge that the definition of *depression* in this trial does not equate to a diagnosis of depressive episode according to accepted criteria, such as those outlined in the DSM-IV[38] and *International Classification of Diseases, 10th Revision* (ICD-10).[39] Therefore, our results should be interpreted as indicative of limited efficacy of B_{12}, B_6, and folic acid to improve symptoms of depression in older men with no or mild to moderate depression. Finally, we did not have systematic access to any history of treatment for depression during the trial, and this may have reduced the power of the study to detect a difference between the groups.

The design of this research project has strengths that also merit comment. Participants were recruited from among a well-established community-representative sample of older men.[31] The randomization and blinding procedures were strictly adhered to, and the overall compliance with trial medication was high. Loss to follow-up was kept within acceptable limits and data were analyzed using a conservative intention-to-treat approach, which was followed by a confirmatory analysis of completers. In addition, treatment was demonstrably effective in increasing the serum concentration of B_{12} and folate and in reducing the concentration of plasma tHcy. Moreover, men with and without depression had similar concentrations of B_{12}, red cell folate, and tHcy at the end of the study, which suggests that the association between vitamins/tHcy and mood is not strong.

Previous observational studies have reported that adults with depression in contact with mental health services have lower concentrations of B vitamins,[12] but community-based surveys have produced conflicting results. Some have described that depression is associated with low concentration of B_{12} but not folate,[15] others with low concentration of folate but not B_{12},[16,18] and yet others with high plasma tHcy independent of the concentration of B_{12}, B_6, and folate.[19,22] The results of previously published trials have also been mixed. Coppen and Bailey[28] conducted the largest trial of folic acid supplementation for the treatment of depression to date. They randomly allocated 127 patients with major depression to fluoxetine plus 500 μg of folic acid or fluoxetine plus placebo for 10 weeks. There was no difference between the groups at the end of treatment on depression ratings (previously published trials are summarized in Table 1).

The rationale supporting the use of B_{12}, B_6, and folate for the treatment and prevention of depression is theoretically attractive. Folate and vitamins B_6 and B_{12} are cofactors in the metabolic pathway that leads to numerous methylation reactions in the brain, some of which seem to be involved in the synthesis of serotonin, norepinephrine, and dopamine.[6] In addition, folate, B_6, and B_{12} vitamin deficiencies are associated with high tHcy, which, in turn, is associated with increased risk of cardiovascular events.[40] Cerebrovascular disease is thought to be an important component of the physiologic process that ultimately leads to the onset and maintenance of depression in later life.[41] However, data from randomized trials do not support this theoretical framework. For example, results from the Norwegian Vitamin (NORVIT) trial showed that treatment with folic acid, B_6, and B_{12} does not significantly reduce the number of cardiovascular events compared with placebo; to the contrary, the 937 adults treated with these vitamins were more likely to experience a fatal or nonfatal cardiovascular event than the 943 people treated with placebo.[42] A similar rationale was applied to reduce the risk of cognitive decline in older people with high tHcy, but the results were equally negative.[43] These results, and those of other trials (e.g., Lonn et al.[44]), indicate that the use of

vitamin B supplements may not be as helpful or as safe as previously thought.

In summary, the results of this double-blind, placebo-controlled trial of B_6, B_{12}, and folic acid showed that treatment with vitamins is no better than placebo in reducing the severity of depressive symptoms and the incidence of clinically significant depression over 2 years. It remains to be determined whether vitamin supplementation would be an effective adjunctive antidepressant treatment for people with severe depression, and if women would benefit more than men from this therapeutic approach.

Drug names: fluoxetine (Prozac and others), lithium (Eskalith, Lithobid, and others), paroxetine (Paxil, Pexeva, and others), sertraline (Zoloft and others), venlafaxine (Effexor and others).

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