

# B Vitamin Supplementation in Treating Depression

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## Abstract

### Objectives:

1. To assess if B vitamin supplementation decreases symptoms of depression.
2. To assess if B vitamin supplementation decreases depressive symptoms in people who take antidepressants yet still experience symptoms of depression.
3. To assess if dietary intake of B vitamins affects the efficacy of B vitamin supplementation in reducing symptoms of depression.

**Participants:** 33 medicated and unmedicated adult students and staff with depressive symptoms at a small regional university in the Midwest, in February 2013.

**Methods:** Participants took a B vitamin supplement daily for 28 days. Presence of depressive symptoms was assessed before and after the intervention using the CES-D Scale. Dietary B vitamin intake was determined by two 24-hour food recalls.

**Results:** There was a significant decrease in depressive symptoms from baseline ( $M = 31.4$ ,  $SD = 9.6$ ) and at post-intervention ( $M = 18.9$ ,  $SD = 10.4$ ),  $t(32) = 7.08$ ,  $p < .001$ , regardless of medication status and dietary intake of B vitamins.

**Conclusions:** This research suggests that B vitamin supplementation may reduce depressive symptoms in people whether medicated or unmedicated with antidepressants, and regardless of their dietary B vitamin intake. Larger, placebo-controlled trials using a B complex supplement are warranted to further investigate B vitamins in treating depression, so that mental health professionals have an alternative or adjunct treatment for patients who are unwilling or unable to take antidepressants, or are responding poorly to traditional treatments.

**Keywords:** B vitamins, B vitamin supplementation, alternative treatment, mental health, depression

## Introduction

By 2020, depression is projected to be the second largest health bur-

den worldwide, with an associated \$150 billion in direct and indirect medical and employment costs. Patient adherence to antidepressant treatment using medications can be as low as 25% because of the negative side effects experienced. In low socio-economic populations, the purchase of and adherence to antidepressant drugs is low, so less expensive options are needed. Treatment-resistant depression is found in more than one third of all people being treated for depression, and over 50% of people who positively respond to antidepressant medications do not experience full remission.

Over 50% of the U.S. adult population uses dietary supplements, and over 60% of people being treated for depression have used supplements. Studies investigating the effects of various supplements on depressive symptoms have revealed conflicting results, and there is limited research on most supplements. Deficiencies of various B vitamins have been associated with psychiatric disorders, including depression. Most studies focus on blood serum correlations of some of the B vitamins and depression. However, only a few of those studies included B vitamin supplementation, and sufficiently randomized double-blind placebo controlled trials are lacking.

The various B vitamins are considered in depression because of their impact in certain mechanisms in the body that are linked to depression. Most of the research has explored vitamin B6, folate, and B12 because they are involved in the synthesis and metabolism of the neurotransmitters and mood hormones serotonin, epinephrine, norepinephrine and dopamine. Serotonin is a neurotransmitter thought to contribute to a sense of happiness and well-being, and epinephrine, norepinephrine and dopamine are involved in mood and behavior. Dopamine is specifically used in the pleasure-reward system of the brain. B6 is involved in the synthesis and metabolism of the neurotransmitter  $\gamma$ -aminobutyric acid (GABA), low levels of which are associated with anxiety and depression. Vitamin B6, folate, and B12 are also involved in homocysteine metabolism, facilitating its conversion into other forms, and thereby reducing the amount of circulating homocysteine in the body. Homocysteine is a marker of inflammation and promotes oxidative stress, and high levels in the body are associated with vascular disease, depression, and can affect neurotransmitter function. In patients being treated with selective serotonin re-uptake inhibitors (SSRIs), better treatment outcomes were associated with patients that had higher serum B12 and folate levels.

Less research exists on the remainder of the B vitamins. Thiamin may be involved in depression due to its function in the nitric system, which plays a role in neuroendocrine responses. It is also involved in the synthesis of serotonin, and decreased serotonin uptake is found with thiamin deficiency. Tryptophan, an essential amino acid, is needed to synthesize serotonin, and it also synthesizes niacin. Niacin supplementation could potentially reduce the need for tryptophan's conversion to niacin, freeing it for serotonin synthesis. Riboflavin is necessary to activate B6 and folate, both

of which are involved in the serotonin-tryptophan pathway. Lastly, true B5 or biotin deficiencies in humans are rare, but when found depression is associated.

White flour fortification of thiamin, riboflavin, niacin and folic acid is mandated in the United States. Despite B vitamin grain fortification, dietary intake of the B vitamins may still be low in some populations. Less than 10% of women of childbearing age meet the recommendation for red blood cell folate concentration, and most oral contraceptive users have low blood plasma levels of vitamin B6 because these medications negatively impact B6 status. Eleven percent of people who take a supplement with B6 have low blood plasma B6 concentrations, and 24% of non-supplement users are low. Older adults are more frequently deficient in vitamin B12 than younger adults due to lower overall food consumption and reduced production of intrinsic factor in the stomach: an important protein required to utilize B12. In one study, eight percent of healthy adults with adequate dietary intake of B12 still had low B12 blood plasma levels. It is possible that some populations may have a deficiency in one or more of the B vitamins even if they are eating the recommended amounts. The dietary reference standards are for healthy people, and people with depression do not fall into that category and are therefore a population in which to consider nutritional deficiencies.

An assessment of the effectiveness of B vitamin supplementation to reduce symptoms of depression in adults could be helpful to ascertain if B vitamins should be considered as adjunct therapy for people already taking antidepressant medications, or for people who are unable or unwilling to take antidepressant medications. The purpose of this research is to investigate the effectiveness of B vitamin supplementation in reducing symptoms of depression. This research explored the following hypotheses:

1. H1: B vitamin supplementation will decrease symptoms of depression.
2. H1: B vitamin supplementation will decrease symptoms of depression in people who take antidepressants yet still experience symptoms of depression.
3. H1: There will be a reduction of depressive symptoms in people regardless of adequate or inadequate B vitamin intake.

## Materials and Methods

### Participants

The IRB of the university, where data was collected, reviewed and approved this study. All subject participation was voluntary. Participants were recruited via advertisements placed on campus, and an email sample of 50% of students and staff from a computer randomized email list made available from the university's research office. The advertisement offered free B vita-

mins for one month, a chance to win a \$50 gift card, and the possibility of a reduction in depressive symptoms. Exclusion criteria included any co-existing psychiatric disorder except anxiety disorders, metabolic conditions or medications that prevented B vitamin usage, regular current use of B vitamins, and pregnant and nursing women.

There were 35 participants at the start of the study, medicated and unmedicated adult students and staff with depressive symptoms. One subject failed to complete the final questionnaire and one subject discontinued the study due to difficulty focusing and a "mild depressive breakdown." Thirty-three participants completed the study including 21 females (63.6%) and 12 males (36.4%). Participant age ranged from 19 to 63 years ( $M = 28.3$ ,  $SD = 13.7$ ), with a median age of 21 years. Participant BMI ranged from 17.9 to 49.0 kg/m<sup>2</sup> ( $M = 28.4$ ,  $SD = 8.3$ ) (Table 1). Twenty-four participants (72.7%) were not taking antidepressant medications and nine participants (27.3%) were taking antidepressant medications which included: Bupropion (Wellbutrin), Citalopram, Fluoxetine (Prozac), Nortriptyline, Sertraline (Zoloft), and Venlafaxine.

Table 1

Participant Body Mass Index (BMI)

BMI Category	Frequency (N=33)	Percentage
< 18.5 Underweight	1	3.0%
18.5 - 24.9 Normal	13	39.4%
25.0 - 29.9 Overweight	7	21.2%
30.0 - 39.9 Obese	7	21.2%
≥ 40.0 Morbid obese	5	15.2%

### Instrumentation

The Center for Epidemiologic Studies Depression (CES-D)36 scale was used to assess depression. A score  $\geq 16$  on the CES-D is considered indicative of clinically significant depression. A questionnaire was created with Qualtrics using the CES-D questions and questions about medication usage, age, gender, alcohol consumption, and smoking status. Alcohol consumption and smoking were assessed because both negatively impact B vitamin usage in the body.<sup>20,37</sup> The CES-D was administered again at the end of the intervention. Two 24-hour food diaries were taken to assess usual B vitamin intake. Participant height and weight was taken to enter into the diet analysis software for BMI calculations to determine the representative weight categories.

The B vitamin supplement given to the participants to consume was a complex called Glycogenics®, developed and manufactured by Metagenics, Inc., headquartered in Aliso Viejo, California. Per the supplement facts panel, each Glycogenics® tablet contains the following B vitamins: thiamin (as thiamin mononitrate) 14 mg (933% Daily Value (DV)); riboflavin 16 mg (941% DV); niacin (as niacinamide and niacin) 200 mg (1000% DV); pantothenic acid (as D-calcium pantothenate) 75 mg (750% DV); vitamin B6 (as pyridoxine HCl) 22 mg (1100% DV); biotin 250 mcg (83% DV); folate (as folic acid and L-5-methyltetrahydrofolate) 400 mcg (100% DV); vitamin B12 (as cyanocobalamin) 250 mcg (4167% DV). Glycogenics® also contains other ingredients to promote B vitamin absorption: vitamin C (as ascorbic acid) 125 mg (208% DV); choline (as choline bitartrate) 100 mg; inositol 94 mg; para-aminobenzoic acid (PABA) 15 mg. Each ingredient was not confirmed by independent testing.

### Procedure

Participants individually met with the researcher at a university laboratory and signed an informed consent form, completed the CES-D questionnaire and questions regarding age, medications, frequency of alcohol consumption, smoking status, and gender. Next, height and weight were measured, and their 24-hour food diary was collected. Participants were then given a 28-day supply of B vitamins with instructions. Participants took one tablet daily for 28 days. Participants received a reminder email and returned 28 days later and completed the post-intervention CES-D questionnaire and comments to report possible positive or negative effects that occurred. A second 24-hour food diary was collected as well as any unused tablets to assess compliance.

### Data Analysis

SPSS 19.0 was used to analyze the data. A paired samples t-test was conducted to determine if there was a significant difference between the participants' baseline CES-D scores and post-intervention CES-D scores. A univariate ANOVA was conducted to assess if there were differences in the reduction of depressive symptoms between the medicated and unmedicated participants, between participants with dietary inadequacy in six or more B vitamins versus those with dietary inadequacy in two or fewer B vitamins, and between male and female participants. Participant gender, age, height and weight were entered into the diet analysis software Food Processor, which was used to determine individual B vitamin needs and to analyze the B vitamin content of subjects' diets. The program compared participants' estimated nutrient needs with actual consumption to assess whether their dietary intake of the B vitamins was adequate or inadequate based on reference standards.

### Results

The range of participant CES-D scores at baseline was 15 to 52 ( $M = 31.4$ ,  $SD = 9.6$ ). One subject had a baseline score of 15, which is less than the generally used cut-off score of 16 that indicates clinically significant depression. A score of 16 was not necessary for the purpose of this study, because a diagnosis or screening for clinical depression was not needed to participate. A paired samples t-test was conducted to compare participant baseline CES-D scores with their post-intervention CES-D scores. There was a significant decrease in participant CES-D scores from baseline ( $M = 31.4$ ,  $SD = 9.6$ ) and at post-intervention ( $M = 18.9$ ,  $SD = 10.4$ ),  $t(32) = 7.08$ ,  $p < .001$  (Figure 1). Hypothesis 1 (H1), that B vitamin supplementation would reduce symptoms of depression, was supported. The effect size,  $d$ , was 1.23, a large effect.

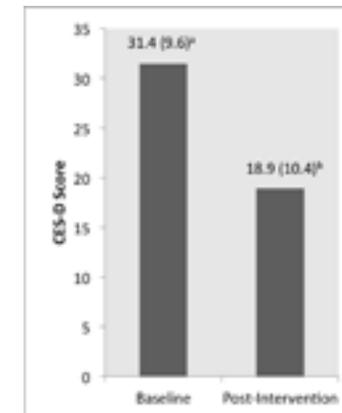


Figure 1. Change in the participants CES-D depression score average from baseline to post-intervention;  $a < b$ ,  $p < .001$ .

There was no significant difference in the reduction of CES-D scores between the medicated ( $N = 9$ ;  $M = -9.22$ ,  $SD = 8.64$ ) and unmedicated ( $N = 24$ ;  $M = -13.62$ ,  $SD = 10.49$ ) participants,  $F(1, 32) = .603$ ,  $p = .445$ , showing that both groups experienced a similar reduction in symptoms of depression. Hypothesis 2 (H2), that B vitamin supplementation would reduce symptoms of depression in people who take antidepressant medication, but still experience symptoms of depression, also was supported. No participant taking medication reported a change, addition, or subtraction to their medications. No participant not taking an antidepressant medication reported starting one during the trial.

Eleven participants (33.3%) had inadequate intake of six or more of the B vitamins, and 22 participants (66.7%) had inadequate intake of two or fewer of the B vitamins (Table 2). There was no significant difference in the reduction of depressive symptoms between the group inadequate in six or more B vitamins ( $M = -14.18$ ,  $SD = 4.05$ ) and the group inadequate in two or

fewer of the B vitamins ( $M = -11.55$ ,  $SD = 12.03$ ),  $F(1, 32) = .058$ ,  $p = .811$ , showing that both groups experienced a similar reduction in symptoms of depression regardless of their dietary B vitamin intake. Hypothesis 3 (H3), that dietary intake of B vitamins would not affect the efficacy of B vitamin supplementation in reducing symptoms of depression, was supported.

Table 2  
Participants Adequacy of Dietary Intake of B Vitamins

B Vitamin	Adequate Intake	Inadequate Intake
B1 (thiamin)	19 (57.6%)	14 (42.4%)
B2 (riboflavin)	20 (60.6%)	13 (39.4%)
B4 (niacin)	26 (78.8%)	7 (21.2%)
B5 (pantothenic acid)	31 (93.3%)	2 (6.7%)
B6 (pyridoxine)	18 (54.5%)	15 (45.5%)
B7 (biotin)	31 (93.3%)	2 (6.7%)
B9 (folic acid)	14 (42.4%)	19 (57.6%)
B12 (cobalamin)	22 (66.7%)	11 (33.3%)

*Note.* N = 33

A supplementary analysis of this research was performed to determine if there were gender differences in the reduction of symptoms of depression, because gender differences in correlations and response to B vitamin supplementation in research is conflicting.14,17,19,28,38 Sometimes only women benefit from higher B vitamin intake, sometimes only men benefit, and sometimes both or neither groups benefit.14,17,19,28,38 There was no significant difference in the reduction of depressive symptoms between women ( $M = -12.67$ ,  $SD = 9.58$ ) and men ( $M = -12.00$ ,  $SD = 11.35$ ),  $F(1, 32) = .007$ ,  $p = .936$ , showing that both groups experienced a similar reduction in depressive symptoms.

## Discussion

The study results support the first hypothesis, that B vitamin supplementation would decrease symptoms of depression, with a significant decrease in depressive symptoms with a large effect size. Participant scores dropped an average 12.5 points on the CES-D scale after taking a B complex vitamin for 28 days. Previous research showed a trend towards a decrease in depressive symptoms with higher B vitamin intake or blood serum values as well as with B vitamin supplementation, but there was also opposing research. The data may conflict because the studies explored three or fewer B vitamins, yet the mechanisms of the B vitamins are often connected. An example is that riboflavin is needed to activate vitamin B6 and folate,20 yet trials with vitamin B6 and/or folate supplementation do not include riboflavin, nor was riboflavin status assessed.9,10,11,19 A search of the EBSCO, PubMed, and

Google Scholar databases revealed no animal or human subject trials using a B complex supplement to treat symptoms of depression. The B vitamin supplement used in this research gave the full complement of B vitamins, which was unlike other similar research, and may be why a positive large effect was found.

The main weakness of this study was that there was no control group with which to compare the treatment group, so it is unknown whether the results are due to the effect of the B vitamin supplement. This is the same weakness encountered in most of the available research on B vitamin supplementation in treating depression. Each participant in this study was informed that there was no expectation that B vitamins would affect depressive symptoms either positively or negatively. In depression studies that have a placebo group, on average, 30% of the participants in the placebo group experience positive effects, and 50% of the participants in the treatment group experience positive effects.39 In this study, over 50% of the participants experienced a significant reduction in their depressive symptoms, although that does not exclude the possibility that the results were due to participant expectations. The large effect size in this study,  $d = 1.23$ , is much larger than the moderate effect sizes found in most depression studies which have a Cohen's  $d$  range of 0.19 to 0.51,40-42 so it is less likely that the improvement in depressive symptoms was due to participant expectation.

The study results support the second hypothesis, that B vitamin supplementation would decrease symptoms of depression in people who take antidepressants yet still experience symptoms of depression, as there was no difference in the reduction of depressive symptoms between medicated and unmedicated groups. The bulk of research in treatment-resistant depression found on the EBSCO, PubMed, and Google Scholar databases focuses on dosage and drug substitution rather than possible nutrition connections, but some individuals described in case studies that were given B vitamin supplementation were able to reduce the dosage and number of their antidepressant medications.13,43

The study results support the third hypothesis, that there would be a reduction of depressive symptoms in people regardless of adequate or inadequate dietary B vitamin intake, with no difference found in the reduction of depressive symptoms between the two groups. Only four participants had adequate dietary intake of all of the B vitamins, achieved by consuming much more than their recommended caloric intake. Overall participant diet quality was poor, but even in participants that had healthier, balanced diets, adequacy in all of the B vitamins was not achieved, which was an unexpected result. This may be due to the study limitation of the two self-reported 24-hour food diaries, as participants may have over or underreported the amount and types of foods consumed. Although 24-hour food recalls and food diaries are considered more accurate than Food Frequency Questionnaires in assessing

average food intake, and studies generally limit the amount of food recalls or diaries taken to no more than three days because of the time consuming nature of the data entry involved,<sup>44</sup> obtaining more food records would have likely improved diet intake accuracy. Measuring the participants' vitamin B blood levels would have improved the study. From the diet results gathered in this study, a B vitamin supplement may be a viable option, because the expectation that most people are able to transform their entire diet to meet their B vitamin needs while not exceeding their caloric requirements may not be realistic for all patients, with consideration to individual lifestyles, severity of depression, and if they have access to, seek out, or are referred to a Registered Dietitian or other qualified licensed nutritionist. This is especially important to consider in patients with vegan and vegetarian diets, and those with poor quality diets, which may be lower in B vitamins. Children may also benefit, as many antidepressants are not approved for use in children, and associations between low B vitamin intake and depression were found in adolescents.<sup>38</sup> Women who take oral contraceptives could also potentially benefit. A side-effect of oral contraceptive use for some women is depression, which may be due in part because oral contraceptives negatively impact B6 status and cause abnormal tryptophan metabolism.<sup>33,45-46</sup> High doses of B6 supplementation were found useful in treating depression in pre-menopausal women and those taking oral contraceptives.<sup>33,45-46</sup>

Each person has a unique metabolism and genetic make-up, and it is possible that some people do not adequately utilize the B vitamins available to them and need a pharmacological dose of one or more of the vitamins, as opposed to simply meeting reference standards. The dosage of B vitamins used in the study was well above the Recommended Dietary Allowance, except for folate and biotin. It may be possible that some people who experience depression cannot meet the quantity of B vitamins needed for optimal health from the diet because there is an underlying metabolic issue or additional disease state that requires a higher B vitamin intake, such as with many gastrointestinal disorders.<sup>20</sup> Metabolic implications are seen in the varying positive and negative effects reported by the participants, such as increased or decreased appetite, increased energy and alertness, and having an easier time waking up in the morning. Although the effects may not be due to the B vitamin supplementation, B vitamins play vital roles in human metabolism. It was beyond the scope of this study was to assess individual participants' ability to absorb the various B vitamins. Assessing the body's efficiency in metabolizing the B vitamins in the depressed person would be an important next step for further research.

Potential confounding factors accounted for were smoking status and alcohol consumption frequency. Cigarette smoking causes depletion in the body of all of the B vitamins,<sup>37</sup> but since only 4 participants smoked, it is unlikely that smoking status influenced the results. Alcohol inhibits the

absorption and utilization of B vitamins (particularly thiamin), increases their excretion, and causes the destruction of some (particularly folic acid).<sup>20</sup> One participant drank nearly every day, followed by a gap in frequency in alcohol consumption to "once or twice a week," with the majority of participants (69.7%) consuming alcohol "once or twice a month" or less. Therefore, it is unlikely that alcohol consumption influenced the results. The two self-reported 24-hour food diaries may be a study limitation, as the amount and types of foods consumed may have been over or underreported. Participant life situations or other unknown variables could have affected the results.

### Conclusions

This research suggests that B vitamin supplementation, particularly a B vitamin complex, may reduce depressive symptoms in people whether medicated or unmedicated, and regardless of dietary B vitamin intake or gender. There is evidence that B vitamins play a role in depression and that supplementation may help alleviate symptoms of depression, but there is little research on B vitamins in the treatment of depression, and very few available trials are human trials. Larger, placebo-controlled trials using a B complex supplement are warranted to further investigate B vitamins in treating depression. Future research could assess if there is a difference in the effectiveness of B vitamin supplementation in reducing symptoms between mild, moderate, and severe depression. Health care professionals should consider B vitamin supplementation in patients who are unwilling or unable to take antidepressants, or are responding poorly to traditional treatments, particularly if a deficiency is assessed through blood tests, or if the patient has poor diet quality or other risk factors. B vitamins are a simple and inexpensive alternative or adjunct treatment option. More studies and conclusive evidence could improve efforts to inform mental health practitioners of the association between nutrition and depression.

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