The Effect of Folic Acid and B_{12} on Depression: Twelve Case Studies

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Abstract

Nutrition plays a vital role in human behavior not just in terms of manifest physical processes but, in particular, nutrition has an impact on individual cognitive and emotional processing. Lack of nutrition or, more specifically, the lack of proper nutrition, is thought to have an adverse effect on mood. The following 12 case studies will explore to what extent incorporating a nutritional supplement into a client's diet impacts the symptoms of persons afflicted with depression. Results from pretest/posttest depression scores using the Beck Depression Inventory-II or the Symptom Checklist-90-Revised will be reported.

Introduction

Recent research has indicated a connection between certain nutritional deficiencies and endogenous depression.[1] Deficiencies in folic acid and cyanocobalamin (vitamin B_{12}) in the system can result in raised concentrations of plasma homocysteine due to the failure of methylation of the homocysteine from the lack of missing nutritional components.[2] Failure to methylate homocysteine can impair monoamine neurotransmitter metabolism.[1] An adequate level of neurotransmitters in the brain, such as serotonin, dopamine, and noradrenaline (norepinephrine), are required for emotional wellbeing.[3] Given the widely held anecdotal belief that modern society is nutritionally deprived, there appears to be initial scientific evidence to suggest an empirical connection between the lack of proper nutrition and the growing prevalence of depression in the general population.[4] In the mid to late 1990s, the World Health Organization (WHO) ranked depression as the fourth most important disorder to address clinically, as the prevalence of depression was the fourth most likely cause of disability and mortality.[5] By 1999, depression had become the number one cause of disability.[4] Treatment efficacy with antidepressant medications has stalled at about 50%, while the use of placebos in experimental research has as nearly an effective treatment outcome at 32%.[6] Some researchers noted that this effect could be directly related to the rise in total homocysteine in our patients, indicating a failure of methylation of homocysteine to methionine due to a shortage of supply of methyl groups from methyl folate or, more rarely in depressed patients, lack of the vitamin B_{12} cofactor for the methylation reaction.[2]

Early research indicated that 56% or more of persons with affective disorders had a folate deficiency.[7] A more recent study indicated that persons with B_{12} deficiency were 70% more likely to have symptoms of severe depression than those without the deficiency.[8] Speculation regarding the effect of nutritional deficiencies on mood appears stable across nationalities,[8] across ethnicity,[9,10] and even gender.[10, 11]

Problem Statement

There appears to be a higher incidence of dysthymic presentations appearing in modern counseling agencies than in previous times.[4] The prevalence of depression in the overall population is approximately "5-8%...[but] later life depression is estimated to be 15%" (p. 59).[6] With only a few notable exceptions, a discussion of the effect of nutritional deficiencies on affect and behavior are nearly missing from modern research, despite the fact that the two constructs have been closely linked together in past research.[12,13,14] In

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addition, there is evidence to suggest that there is a mild to moderate correlation between nutritional problems in individuals and their subsequent presenting mood disruptions.[15,16]

It is important to recognize that if nutritional deficiencies are causal to symptoms of depression that the likelihood of an actual cure for the symptoms of depression with antidepressant medication, or with talk therapy for that matter, is very low. Since folic acid and cyanocobalamin deficiencies have been identified as highly probable in affecting other neuropsychiatric disorders,[2] and cyanocobalamin deficiency has been related to histadelic (or high histamine) related schizophrenia-like symptoms,[17] this research was designed to address the question of whether these specific deficiencies are related to symptoms of depression, and whether or not the symptoms can be corrected with a nutritional supplement. Since "folic acid deficiency is one of the most common nutritional deficiencies in the world" (p. 721),[18] it is indeed time to re-explore to what exact extent the nutritional supplements folic acid and vitamin B_{12} can be employed to alleviate symptoms of depression.

Significance of the Study

If indeed the symptoms of depression can be stabilized with a common vitamin or nutritional supplement, then the need for an unnecessary invasive allopathic medication in the system could be reduced. While it is prudent to be cautious when exploring alternatives to conventional medicines for the treatment of depression,[19] the need to explore the effect of proper nutrition on negative affective states is overdue. If symptoms of depression can be corrected with non-invasive, orthomolecular treatment such as a nutritional supplement rather than a synthesized medication, the implications for modern medicine would be staggering. Further, if some forms of depression are resistant to antidepressant medication due to the lack of proper nutrition, then too, talk therapy will be futile in the face of the nutritional deficiency. This is a significant issue to address, research, and resolve in terms of professional counseling therapy, psychiatry, and even general practice medicine.

In light of the above, the importance of this type of research becomes evident. Given that (a) a growing number of people are being prescribed antidepressant medications (that at best work at the 50% rate reported above), and, (b) a number of mood disorder symptoms are likely attributable to some form of nutritional deficiency, then it becomes imperative to determine if symptoms of depression can be reduced with a nutritional supplement rather than having to treat the depression with a medication. Currently, the American Psychiatric Association (APA) defines dysthymic disorder in the Diagnostic and Statistical Manual of Mental Disorders (DSM-IV-TR)20 as a cluster of symptoms that include (a) changes in appetite, (b) changes in sleep patterns, (c) decreased energy, (d) reduced self-esteem, (e) cognitive disruptions, and, (f) feelings of hopelessness. There are also severity and longitudinal specifiers in the DSM-IV-TR, as well as other specific criteria to clarify a differential diagnosis. Given the need to clinically assess the physical status of the client as well as the mental and experiential conditions present with his or her depression, combined with the growing body of evidence that symptoms of depression can be linked with physical causes, it is difficult to understand why the notion of proper nutrition is overlooked in the DSM-IV-TR as a potential causal property of dysthymic affect.

Research Question

The research question to be considered is; to what extent will individual symptomatic levels of depression be impacted by the inclusion of a nutritional supplement in their diet? The independent

variable identified for this study was the incorporation of a nutritional supplement into the diets of the case study group. The dependent variable was the concept measured by testing instruments used (i.e., reported level of depression).

Definition of Terms

For the following terms, note that all definitions are taken from Dorland's Illustrated Medical Dictionary,[21] except chemical compound structures, which are taken from Webster's New World Dictionary.[22] Folic acid ($C_{19}H_{19}N_7O_6$), is a water-soluble vitamin that helps to regulate the level of homocysteine in the blood, and is a single carbon transfer coenzyme that is required for methylation of homocysteine. Folic acid is also used in treating anemia. Cyanocobalamin ($C_{63}H_{88}CoN_{14}O_{14}P$), also known as vitamin B$_{12}$, is also a water-soluble, externally obtained vitamin that participates in coenzyme catalyzed reactions and methyl group transfers. Cyanocobalamin is also required for the methylation of homocysteine as is folic acid, but to a lesser degree.

In this context, a nutritional supplement is whatever appropriate combination of naturally occurring substances that are introduced into the system to correct for a nutritional deficiency in the participants of the research. Homocysteine, which is formed after the digestion of protein rich foods, is a necessary but toxic amino acid. Abnormally high levels in the blood are believed to produce cardiovascular disease, stroke, atherosclerosis, complications in pregnancy, and disturbances in mood. Excesses are caused either by improper nutrition or by the congenital passing of a recessive gene. Methionine ($C_5H_{11}NO_2S$) is an exogenously obtained sulfur-containing essential amino acid used in the production of protein. Methionine reacts with adenosine triphosphate in the body to produce S-adenosyl methionine, or SAMe, a potent donor of methyl

groups in the synthesis of norepinephrine. Methylation is the process by which enzymes are calalyzed to regulate protein functions, and results in the conversion of cytosine to 5-methlycytosine, a methyl group contributor.

Serotonin ($C_{10}H_{12}N_2O$) is a neurotransmitter found in blood platelets that is formed from tryptophan, that helps regulate cyclic physical processes and mood. Serotonin constricts the blood vessels, helps to contract smooth muscle tissue, and is important both as a hormone and as a neurotransmitter. Norepinephrine ($C_8H_{11}NO_3$), also referred to as noradrenaline, is an adrenaline-related neurotransmitter and hormone that belongs to a class of endogenous chemicals known as catacholamines that control heart rate, blood pressure, and stabilizes mood. Norepinephrine is secreted by the adrenal medulla, is used by the body to constrict blood vessels, stop bleeding, and is liberated at nerve endings to help transmit nerve impulses.

Assumptions and Limitations

Based on the growing number of peer-reviewed journal articles published that support the notion that folic acid and cyanocobalamin have a direct influence on homocysteine levels, and thus depression, it was assumed that each of the participants had an equal level of plasma homocysteine. Limitations of the study would thus include the problem of defining whether or not the participant's blood plasma homocysteine levels were abnormal. To test each participant would have been financially prohibitive, and thus each participant was treated as having equal levels. Since the purpose of this research was only to determine at what level the nutritional supplement impacted levels depression (rather than homocysteine levels), the results would still be generalizable and transferable to larger populations with depression. Addition-

ally, since the study could not be held in a completely controlled environment there could be other nuisance or confounding variables that affected the outcome of the research, thus providing another limitation to the study. The participants of the research were in outpatient therapy at the time of the study, and thus the separation of treatments (i.e., nutritional supplement and talk therapy) could not be established.

Sample

The study used a non-random purposive sample for unique cases to identify the target sub-population of individuals diagnosed with depression. The sample consisted of 12 adult men (n = 4) and adult women (n = 8) who were attending outpatient therapy at a local mental health agency. Ages ranged from 29 to 59-years-old, and each of the participants had a diagnosis of dysthymic disorder. Each participant was provided with informed consent prior to the research, and each participant volunteered for the study.

Nutritional Supplements

The nutritional supplements used in this study were folic acid and vitamin B_{12} in the following dosages. Folic acid was taken in an 800 mcg tablet once per day in the morning. Vitamin B_{12} was used in 500 mcg tablets twice per day, one in the morning with the folic acid, and one at noon. Note that any participant in the study who was prescribed an antidepressant medication prior to the research remained on the medication throughout the trial.

Instrumentation

The instruments used to measure the levels of depression in the sample were the Beck Depression Inventory-II[23] or the Symptom Checklist-90-Revised.[24] The BDI-II is a 21-item, forced-choice, self-report instrument for the assessment of symptoms and attitudes of depression quite similar to the criteria set forth by the APA. Possible scores for the BDI-II can range from zero to 63. Scores under 13 are considered minimal for depression. Scores between 14 to 19 are identified as mild, scores between 20 and 28 reflect moderate depression, and scores at 29 or above are to be interpreted as severe. Content validity of the BDI-II is high, as the instrument was specifically designed to reflect the criteria of the DSM-IV, and construct and convergent validity was tested against the previous version of the instrument (r = .93, p < .001). In anticipation of questions regarding the rationale for selecting the BDI-II over other measures of depressive tendency, the BDI-II is the most current in terms of contemporary norms, and it was designed to specifically test the DSM criteria for depression. Additionally, the BDI-II has companion inventory-specific computer software[25] that can quickly calculate t-scores and percentiles, as well as automatically calculate what level of change needs to occur in individual scores to be considered significant at the .05 level.

The Symptom Checklist-90-R (SCL-90-R) is a 90-item forced-choice self-report instrument designed to assess a broad spectrum of symptoms, and one subscale specifically evaluates depression. Content validity of the SCL-90-R is high, as the depression subscale was highly correlated with other measures of depression that reflect the DSM criteria. Construct and convergent validity shows strong factorial invariance with other subscales, with high test-retest values in three different studies (r = .90, .75, and .85, respectively; p. 27).[24] The SCL-90-R provides a raw score (the subscale total divided by the number of endorsed items of the subscale), and a standardized t-score for comparison to the reported normative sample in the manual.

The rationale for using two testing

instruments is based on (a) the logical assumption that instrumentation specificity could potentially confound the results, and, (b) the results of both of these instruments report a t-score appropriate for comparison. A six-week test-retest period was used to (a) have enough time to minimize the potential for the placebo effect, (b) have enough time to reduce the potential for test-retest effect, and, (c) limit the amount of time for therapy to confound the study's outcome. Regarding one of the participants, no retest information can be provided as he left the trial early. That and any other condition that could have effected the study will be discussed below.

Case Studies

Richard, a 56-year-old Caucasian male, presented for treatment with depression and anger management issues. He reported not having any satisfaction with life, and felt "moody" and angry all the time. His initial SCL-90-R depression subscale score was significantly elevated (R = 1.31, T = 71) indicating clinical depression. A six-week retest after beginning the treatment with folic acid and B_{12} indicated reduced raw and t score (R = .85, T = 64), placing his t score just beyond the first standard deviation. His retest score did indicate the continued presence of clinical depression (above T = 63 for the SCL-90-R), but the reduction of depressive symptoms and affective distress in Richard was evident.

Linda, a 45-year-old Caucasian female, presented for treatment with a high-moderate level of depression as evidenced by a BDI-II raw score of 27 (T = 80). She was referred by her primary healthcare physician after the prescribed antidepressant medication (Paxil) had failed to control her symptoms in a six month follow-up. She presented as labile, ruminating, and reported being barely able to control her emotions in public or at home. Linda continued to take her medication during the trial, and her six-week retest after beginning treatment with folic acid and B_{12} indicated a significantly reduced score on the BDI-II (R = 9, T = 55), placing her level of depression in the minimal range after treatment.

Arthur, a 52-year-old Caucasian male, presented with clinical depression and mild anxiety, and stated that he would not take antidepressant medication if prescribed. He reported being agitated and feeling "down" most of the time. His initial SCL-90-R score indicated the presence of mild depression (R = .85, T = 65). After beginning the folic acid and B_{12} treatment, he left outpatient treatment after only four weeks, stating that he no longer felt depressed or anxious, and felt as if he no longer needed therapy. Unfortunately, no test-retest information is available for this case, but Arthur's subjective report of reduced symptoms of depression can be accepted anecdotally.

Alicia, a 52-year-old African-American female, presented as clinically depressed with strong seasonal affective features. She was referred by her primary healthcare physician after the prescribed antidepressant medication (Wellbutrin) had failed to control her symptoms in a nine month follow-up with her doctor. She reported feeling sad most of the time, was crying at random intervals for non-specific reasons, and had begun isolating herself from her family and friends. Her initial SCL-90-R results indicated a significant level of depression (R = 2.62, T = 74). Alicia continued to take her medication during the trial, and her retest after six weeks on folic acid and B_{12} indicated a significant reduction in symptoms (R = .38, T = 52). It should be noted that this trial took place during the season of her primary affective distress.

Karl, a 59-year-old Caucasian male, came to treatment suffering from chronic severe depression. Karl was referred to

psychotherapy by his primary healthcare physician after the prescribed antidepressant medication (Wellbutrin) had failed to control his symptoms after one year. Karl reported being sad and lethargic most of the time, and "angry at the world" the rest of the time. His initial SCL-90-R depression subscale score indicated a significant level of depression (R = 2.31, T = 81). Karl also continued to take his medication during the trial, and his retest after six weeks on folic acid and B_{12} indicated a reduced level of depression (R = 1.23, T = 71). His retest score on the SCL-90-R still indicated a clinical level of depression, but the reduction of symptoms from beyond the third standard deviation to just beyond the second is important.

Nancy, a 35-year-old Caucasian female, came to therapy suffering from short-term severe depression and a high level of situational stress. She reported having intense mood swings, uncontrollable emotional outbursts, feeling "burned out," and a very low tolerance to and kind of frustration. Her initial BDI-II score confirmed the presence of a severe level of depression (R = 30, T = 85). Nancy attended only a few therapy sessions during the trial, but her retest after six weeks on folic acid and B_{12} still indicated a significant reduction in her raw and t-scores (R = 12, T = 59).

John, a 49-year-old Caucasian male, presented with short-term clinical depression that he attributed to ongoing circumstantial life events. His initial BDI-II score indicated a high-mild level of depression (R = 19, T = 69), bordering on moderate depression. John also only attended a few therapy sessions during this trial, and his retest after six weeks on folic acid and B_{12} did indicate a substantial reduction in his raw and t-scores (R = 7, T = 52). These last two cases are especially important because they are less affected by other confounding variables than the rest, and yet both cases still resulted in a reduction of symptoms.

Alexia, a 52-year-old Caucasian female, presented with chronic clinical depression confounded by multiple psychosocial stressors. She was referred by her primary healthcare physician for psychotherapy after the prescribed antidepressant medication (Lexapro) had failed to control her symptoms in a one-year follow-up. She reported crying constantly, a general loss of interest in things she used to enjoy, and was extremely labile at intake. Her initial BDI-II score confirmed a severe level of depression (R = 34, T = 90). She continued to take her medication during the trial, and her retest after six weeks on folic acid and B_{12} indicated a significant reduction in reported symptoms measured by the BDI-II (R = 15, T = 63).

Barbara, a 47-year-old Caucasian female, presented with chronic clinical depression referred by her primary healthcare physician for therapy after the prescribed antidepressant medication (Paxil) had failed to control her symptoms in a one year follow-up. She reported being unable to control her mood, that she was crying constantly, and observationally, she was extremely labile at intake. Barbara's is one of three cases where both a BDI-II and an SCL-90-R score were available. Her initial BDI-II score confirmed the presence of a severe level of depression (R = 42, T = 100). Her initial SCL-90-R score was also elevated (R = 2.92, T = 75). She continued to take her medication during the trial, and her six-week retest after beginning the treatment with folic acid and B_{12} indicated a reduced score on the BDI-II (R = 8, T = 53) as well as a reduction on her reported symptoms on the SCL-90-R (R = 1.08, T = 62).

Helen, a 37-year-old Caucasian female, was referred by her primary healthcare physician for psychotherapy after the prescribed antidepressant medication (Zoloft) had failed to control her symptoms in a six-month follow-up. Despite the use of her medication, she reported being sad, fatigued, and angry most of the

time. Helen's initial BDI-II score placed her level of depression in the severe range (R = 38, T = 96). She continued to take her medication during the trial, and her six-week retest after beginning the treatment with folic acid and B$_{12}$ indicated less symptoms through a reduced BDI-II score (R = 11, T = 57). Helen's is the second case where pre- and posttest SCL-90-R results also exist (pretest: R = 2.92, T = 75; posttest: R = 1.15, T = 63).

Jessica, a 29-year-old Caucasian female, presented with long-term chronic depression and associated anxiety. She also had been referred by her primary healthcare physician for psychotherapy after the prescribed antidepressant medication (Prozac) had failed to control her symptoms in a nine-month follow-up. Despite the use of her medication, she reported feeling extremely sad and agitated most of the time, with accompanying fatigue. Her initial BDI-II score placed her level of depression in the severe range (R = 33, T = 89). Jessica is the third participant whose case file also had an SCL-90-R assessment available (R = 3.00, T = 76). She continued to take her medication, and her retest after six weeks on folic acid and B$_{12}$ indicated a reduction in raw and t-scores for the BDI-II (R = 22, T = 73) and the SCL-90-R (R = 1.69, T = 68). While there is a significant difference between the pretest t-scores of the SCL-90-R and the BDI-II, the posttest scores of the two instruments are similar.

Finally, Roxanne, a 45-year-old Caucasian female, presented with long-term chronic depression. She self-motivated to enter outpatient treatment after her antidepressant medication (Paxil) reportedly began to "lose its effect" in controlling her symptoms. She reported feeling disconnected from herself, as if a "black cloud" or a "void" was around her at all times. Roxanne's initial SCL-90-R depression subscale score was elevated (R = 1.92, T = 74). She continued to take her medication during the trial, and her retest after six weeks on folic acid and B$_{12}$ indicated a decrease in reported symptoms of depression (R = .69, T = 58).

Discussion

The raw and t-scores of each of the participants indicated a reduction in reported levels of symptoms of depression. The t-score reduction ranged from −16 to −47 on the BDI-II, and the SCL-90-R t-score reductions ranged from −seven to −22. For the case study participants where both BDI-II and SCL-90-R assessments were available, the differences in pretest t-scores scores were unusual, with the BDI-II pretest mean being significantly higher (T = 87) than the SCL-90-R (T = 75.1). The difference of the pretest results of the two instruments could be attributable to the specificity of the BDI-II in screening for depression as opposed to the SCL-90-R which is used more for assessing wide-ranging psychological symptoms. Posttest scores from both instruments were similar, however, and showed an overall reduction in the reported levels of depression across the sample (BDI-II posttest mean T score = 58.9; SCL-90-R posttest mean T score = 62.6). As a whole, the group's t-score averages for the reported levels of depression were reduced 20.4 points (see **Table 1, P.8**). Both the BDI-II and the SCL-90-R testing instruments indicated this overall reduction of symptoms of depression in separated results (see **Table 2, P.8**).

The findings of this research are of course limited based on the small size of the case study sample. However, the results are also important in terms of adding to the knowledge base regarding the potential benefits of folic acid and B$_{12}$ supplements in the treatment of depression. In some cases, the effect of the supplements still failed to reduce symptoms below clinically diagnosable levels, but in those cases, antidepressants

Table 1. Participant Pre- and Post-test BDI-II and SCL-90-R T-Scores (N = 11)

Participant	Pretest	Post-test	Reduction
Richard (S)	71	64	-7
Linda (B)	80	55	-25
Alicia (S)	74	52	-22
Karl (S)	81	71	-10
Nancy (B)	85	59	-26
John (B)	69	52	-17
Alexia (B)	90	63	-27
Barbara (B)	100	53	-47
Barbara (S)	75	62	-13
Helen (B)	96	57	-39
Helen (S)	75	63	-12
Jessica (B)	89	73	-16
Jessica (S)	76	68	-8
Roxanne (S)	74	58	-16
Mean T-Score	81.1	60.7	-20.4

Note. (B) = BDI-II   (S) = SCL-90-R

Table 2. BDI-II (n = 7) and SCL-90-R (n = 7) Pre- and Post-test T-Scores with Reductions (N = 11)

	BDI-II				SCL-90-R		
	Pretest	Post-test	Reduction		Pretest	Post-test	Reduction
Linda	80	55	-25	Richard	71	64	-7
Nancy	85	59	-26	Alicia	74	52	-22
John	69	52	-17	Karl	81	71	-10
Alexia	90	63	-27	Roxanne	74	58	-16
Barbara	100	53	-47	Barbara	75	62	-13
Helen	96	57	-39	Helen	75	63	-12
Jessica	89	73	-16	Jessica	76	68	-8
Mean	87.0	58.9	-28.1	Mean	75.1	62.6	-12.6

Note. BDI-II = Beck Depression Inventory-II   SCL-90-R = Symptom Checklist-90-R

had also previously failed to reduce those symptoms. Given that the greatest effect appeared in the participants who were already on antidepressant medication without relief from their symptoms, one can infer that it was the effect of the supplements rather than the effect of the medications that were responsible for the reduction in the participant's symptoms, although one cannot reject cross-benefits from potentiation.

The purpose of this research was only to determine the impact of the specified supplements on depression, and each participant was treated as having equal levels homocysteine. The more affected cases might have had levels of homocysteine that were abnormal but that will remain undetermined. Although not all variables could be controlled, which may have confounded the results, this study justifies the need to create a clinical trial to empirically assess the potential benefit of using these supplements with depressed clients. To the point, an experimental design using a non-random, purposive, stratified sample randomly assigned to three groups would be necessary (i.e., an experimental group, a placebo group, and a control group). Experimental designs typically have very high internal and external validity if the threats to external validity (i.e., history, maturity, testing practice effect, etc.) are sufficiently controlled by the researcher. The experimental method is the only true way in which to deduce causation and infer the probability of the results.

Conclusion

The results of this research indicated that folic acid and B_{12} nutritional supplements did indeed play a significant role in decreasing the symptoms of depression reported by the participants. Thus, the findings of this study indicate a need for further scientific research with a broader sample in a more controlled trial. A reported reduction in the symptoms of depression in each of the participants of this study justifies that conclusion.

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