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Effects of B Vitamins on Symptoms and Cognitive Functions in Schizophrenia: A Randomized, Double-Blind, Placebo-Controlled Clinical Trial

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Abstract

Objective: Schizophrenia which is a chronic disabling burdensome psychotic disorder has been treated with different antipsychotic medications. Some studies have reported a possible correlation between deficiency in minerals, nutrients and vitamins — mainly group B vitamins — and the development of schizophrenia. In the present study, we aimed to examine the effect of the B vitamin group as an adjuvant treatment to antipsychotics in individuals with chronic schizophrenia.
Method: In a randomized, double-blind clinical trial study, involving two groups of 25 patients with chronic schizophrenia, we compared the effects of a 12-week adjuvant treatment with a combination of B vitamins — B1 (15mg), B2 (15mg), B6 (10mg), B12 (10µg) and nicotinamide (50 mg) — with a placebo. The impact on negative, positive and cognitive symptoms of schizophrenia was assessed for both groups before the intervention (T0) and at 4, 8 and 12 weeks after the intervention (T1, T2, and T3, respectively).
Results: Following the treatment, negative symptoms scores decreased in the treatment group at 12 weeks following the beginning of the treatment ($F(4, 45) = 464.7$, $P < 0.0001$). Although a trend toward improvement in positive symptoms and cognitive scores was seen, these changes were not significant.
Conclusion: Our results suggest that selecting the group B vitamins as an adjuvant treatment to the antipsychotics may have beneficial effects on improving negative symptoms of patients with chronic schizophrenia.

Key words: *B Vitamins; Clinical Trial; Cognition; Psychotic Disorder; Schizophrenia*

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Schizophrenia is a psychotic disorder of high prevalence and severity (1) which has a profound effect on the lives of patients, their families, and society at large (2). It is considered one of the most incapacitating and financially burdensome chronic illnesses on a global scale (3). The estimated lifetime prevalence of schizophrenia is approximately 0.28% worldwide. This condition contributes to a total of 3.4 million years of life experienced with disability (YLDs) (4).

The diagnostic criteria of schizophrenia are mentioned in the 5th edition of the Diagnostic and Statistical Manual of Mental Disorders, (DSM-5) (5) as follows: the presence of both positive symptoms, particularly delusions, hallucinations, and disorganized behavior, and negative symptoms, including deficit in emotional expression, social withdrawal, social amotivation, and anhedonia. In addition to positive and negative symptoms, a majority of individuals with schizophrenia (approximately 75-80%) manifest impairments in cognitive functions. Cognitive impairment is mainly observed in executive functions, processing speed, attention, problem-solving, memory, verbal fluency, and social cognition (6). These symptoms are contributing factors to unfavorable clinical consequences, such as unemployment and inability to maintain an independent lifestyle (7).

Treatment of schizophrenia, according to the American Psychiatric Association (APA) recommendation, is based on antipsychotic medication. Patients should be monitored regularly for effectiveness and side effects of antipsychotics (8, 9). It is notable that antipsychotic treatment is mainly demonstrated effectiveness in achieving remission of positive symptoms; while negative symptoms and impairment in cognitive functions do not usually improve using antipsychotic medications (3). Although different psychological treatments like cognitive behavioral therapy (CBT) (10) and cognitive rehabilitation strategies (11) are suggested to decrease remaining symptoms in patients with schizophrenia, these methods are not easily accessible and affordable for a large number of patients (3).

An increasing collection of studies, in the recent years, has reported potential associations between nutritional deficiencies and an elevated susceptibility to schizophrenia. The results of these studies have shown correlations between vitamins and minerals deficiency, low serum amino acid levels and dietary fatty acid intake and an increased risk of schizophrenia (1). Insufficiency in vitamin D and group B vitamins are shown to have been associated with the intensity of schizophrenia symptoms. This association is more prominent in negative symptoms and neurological abnormalities such as hippocampal deterioration and cognitive dysfunction (3).

Besides the role of these elements in neurometabolism and biosynthesis of proteins, their anti-inflammatory and antioxidant properties are important factors in using these elements for treating schizophrenia (3). Previous studies have shown that using high doses of vitamin B or combinations of B-group vitamins to be effective in reducing psychiatric symptoms. For instance, one study (12) reported a reduction in positive symptoms using a combination of B-group vitamins, especially in a subgroup with hyperhomocysteinemia. Other studies (13, 14) reported that folic acid administration in a group of patients with impaired folate absorption improved negative symptoms. The beneficial effects of these supplements are primarily observed when they are used early in the course of the disease (3).

Compelling evidence has been showing the relationship of folic acid or vitamins B6 and B12 with occurrence and development of schizophrenia; however, it remains unclear whether other subgroups of vitamin B were involved in this process (15).

While earlier research has investigated the impacts of group B vitamins on patients with schizophrenia, the focus of such studies has been especially on folic acid and B12. In addition to the lack of research on the effects of other vitamin B subgroups, most studies have been conducted on individuals encountering their initial episode of psychosis, and there is a lack of research on other patients such as chronic schizophrenia (16).

Given the lack of sufficient research in this area, we intended to examine the impact of a combination of group B vitamins, including vitamins B1, B2, B6, B12 and nicotinamide as adjuvant therapy along with antipsychotic medication on individuals with chronic schizophrenia. The present study is designed as a double-blind randomized clinical trial to compare the impact of the above-mentioned vitamin combinations and placebo on both negative and positive symptoms of these patients, as well as on cognitive functions scores.

Materials and Methods

Participants

We have recruited individuals diagnosed with schizophrenia through a structured interview and have been hospitalized in chronic care and rehabilitation service in Razi Psychiatric hospital in Tehran, Iran, between January 1, 2022 and May 1, 2022.

The inclusion criteria included hospitalized patients with schizophrenia (diagnosed in a structured interview by a psychiatrist based on DSM-5 criteria (5)). They were aged between 18 and 65 years old, had a minimum education level of 5 grades, without any other psychiatric comorbidities. They also had no any severe medical conditions based on medical records and examination, no drug or medication abuse during the last 6 months and, and no electroconvulsive therapy (ECT) in the last two months. Moreover, patients had no contraindication or allergy to vitamin B, were on antipsychotic monotherapy with Risperidone, Quetiapine or Aripiprazole, and had an IQ score above 70 as evaluated by Raven's progressive matrices test.

The exclusion criteria consisted of the need for changing antipsychotic treatment for any reason during the study, using both typical and atypical antipsychotic at the same time, and the presence of adverse effects.

The calculated sample size using G-power (17), considering a power of 80%, a significance level of 0.05, and an effect size of 0.44 based on previous studies, required a total of 50 participants, i.e. 25 per group. Figure 1 shows the flowchart of subject recruitment and follow-up steps.

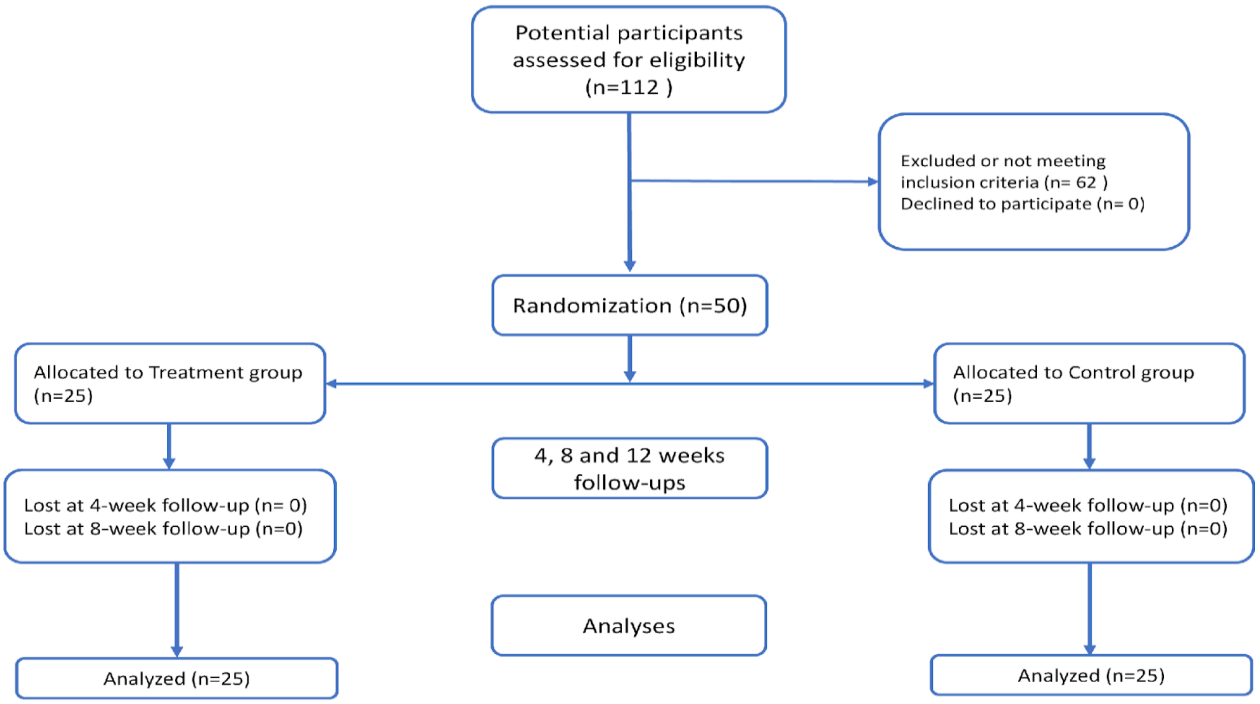

Figure 1. Flowchart of Participant Recruitment and Stages of Study Follow-up.

Study Procedure

In this double-blind, parallel-group, placebo-controlled randomized clinical trial, a sum of 50 patients with chronic schizophrenia who met the inclusion criteria were recruited (see section Participants for details of the inclusion criteria). Using an Excel RAND function, the patients were allocated with random assignment to two groups: the control group (n = 25) and the treatment group (n = 25). Allocation to the groups was hidden from the researchers and patients.

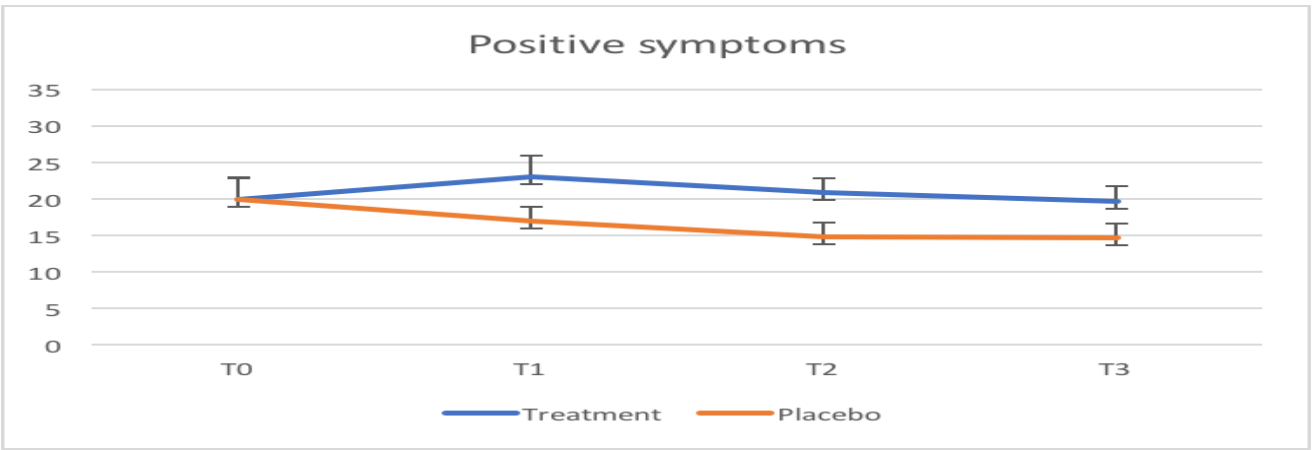

Figure 2. Changes in Positive Symptoms at Different Time Points: Before and at Four, Eight, and Twelve Weeks of Treatment

T0: Before treatment, T1: At 4 weeks of treatment, T2: At 8 weeks of treatment, T3: At 12 weeks of treatment.

In addition to their prescribed antipsychotic monotherapy, the participants of the treatment group took one capsule per day containing Group B vitamins including vitamins B1 (15mg), B2 (15mg), B6 (10mg), B12 (10µg) and nicotinamide (50 mg). This combination of group B vitamins was selected under the supervision of a clinical pharmacy specialist.

Patients in the control group took one placebo capsule per day, which was similar to vitamin B combination capsule in shape, color, weight, smell and taste, in addition to their prescribed antipsychotic monotherapy. Patients, researchers, and primary investigator of the study were blind to the type of capsules. This intervention was carried out during a 12-week period both for the treatment and control groups. Schizophrenia symptoms assessment were carried out using Positive and Negative Syndrome Scale (PANSS) and Montreal Cognitive Assessment (MoCA) at four time points: prior to the intervention (T0), at four weeks (T1), eight weeks (T2), and twelve weeks (T3) following the start of the intervention. Group B vitamin levels were measured at T0 and T3 in both groups. Any adverse effects of the treatment were also evaluated.

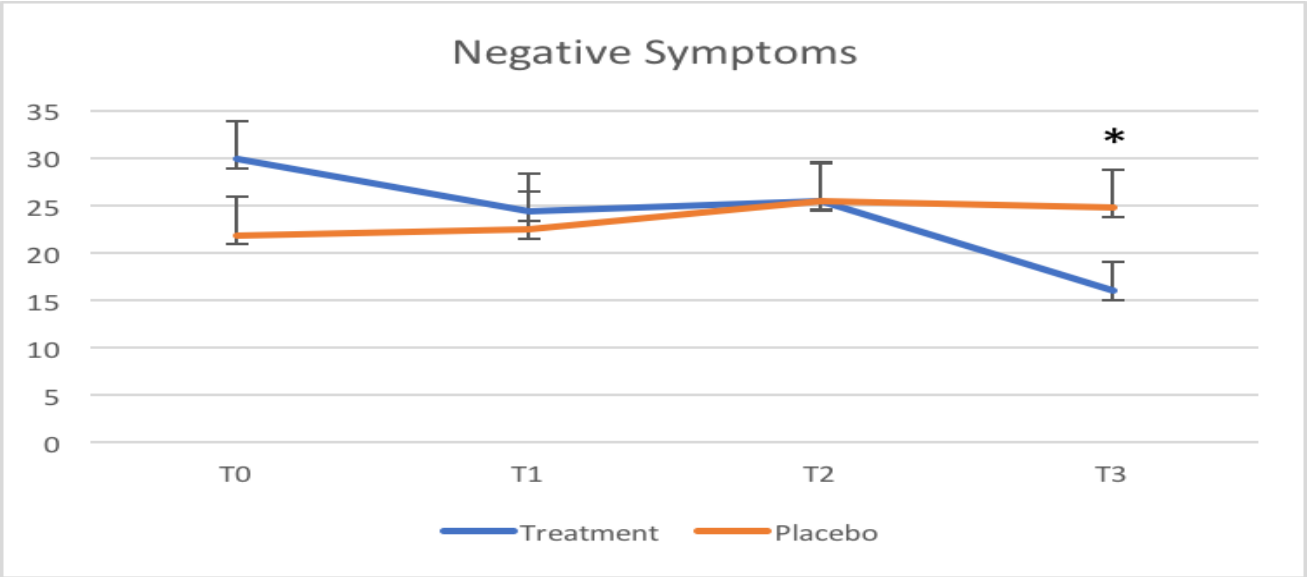

Figure 3. Changes in Negative Symptoms at Different Time Points: Before Treatment and at Four, Eight, and Twelve Weeks of Treatment

T0: Before treatment, T1: At 4 weeks of treatment, T2: At 8 weeks of treatment, T3: At 12 weeks of treatment.
There was a significant difference between the two groups at T3. * P < 0.05

Assessments and Measures

The Criteria for Schizophreniabased on DSM-5

As stated in the DSM-5 (5), the criteria for diagnosing schizophrenia requires the presence of at least two symptoms from the following: hallucinations, delusions, disorganized or catatonic behavior, disorganized speech, and negative symptoms. Furthermore, at least one of these symptoms must involve hallucination, delusions, or disorganized speech. The indicators of disturbance should persist for a minimum of 6 months. This period of 6 months should encompass a duration of symptoms for at least one month (or shorter if effectively treated) that align with the previously stated criteria (i.e., symptoms occurring during the active phase). Impaired function in interpersonal relations, self-care, social or occupational occurs for a considerable duration. These problems must not be linked to the physical consequences of substance use or any other medical issue. Schizoaffective disorder and mood disorder with psychotic features need to be excluded.

Raven' Progressive Matrices Test

Raven's Progressive Matrices (RPM) is a non-verbal assessment commonly utilized to evaluate general human intelligence and abstract thinking. It is one of the most frequently conducted tests in different age groups ranging from 5-year-olds to the elderly. RPM comprises 60 multiple-choice questions arranged by in ascending level of difficulty. The retest reliability coefficient of this test is reported to be 0.82 (18).

All potential participants performed this test while observed by a trained psychologist, once prior to the beginning of the intervention. Patients with an RPM score of above 70 were included in the study.

Positive and Negative Syndrome Scale (PANSS) for Schizophrenia

We used the Persian version of the PANSS. The PANSS is a 30-item clinician-administered rating scale which is frequently used for evaluating the severity schizophrenia symptoms. The administered PANSS includes five subscales: Positive scale (six questions), Negative scale (eight questions), Disorganized Behavior scale (seven

questions), Excitement scale (four questions), and Emotional Distress scale (five questions). Each subscale is rated with a Likert scale of 1 to 7 points (ranging the intensity of symptoms from absent to extreme). This scale has an acceptable construct validity and the Cronbach's alpha reliability coefficient of this scale is reported to be 0.8 (19). This evaluation was performed at T0, T1, T2, and T3.

Montreal Cognitive Assessment (MoCA)

The MoCA is recognized as a brief tool, with high sensitivity for evaluating cognitive functions and screening cognitive impairments. This tool has been commonly utilized in various clinical environments and has high sensitivity and specificity in identifying mild cognitive impairments (20). We have administered the Persian version of the MoCA test at T0, T1, T2, and T3.

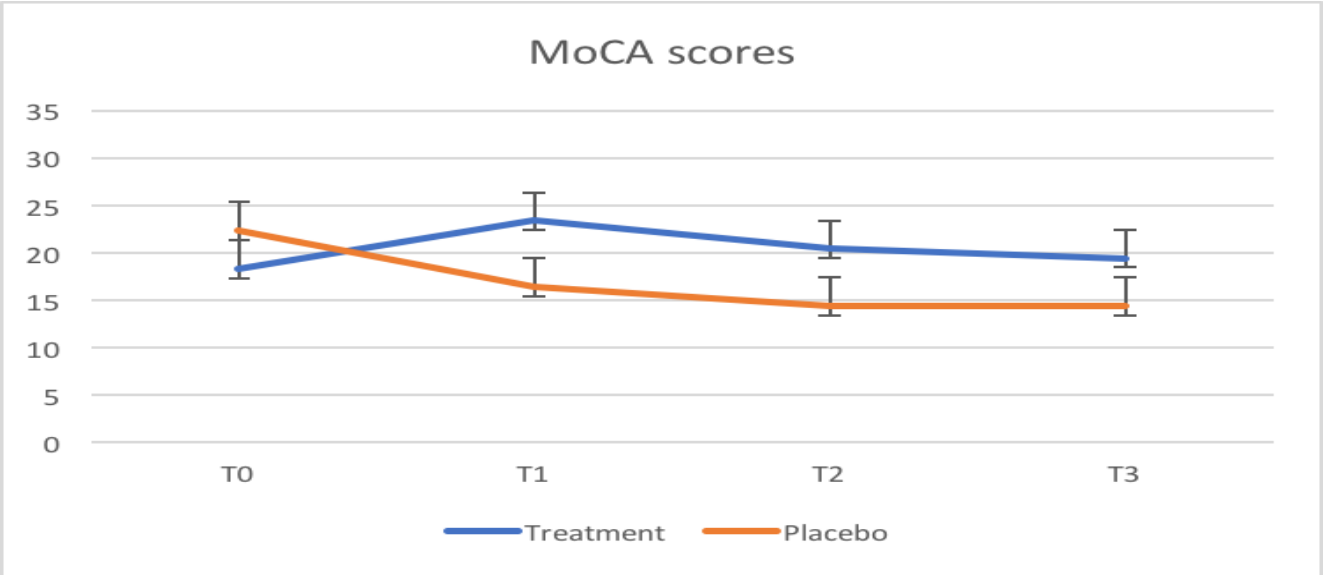

Figure 4. Changes in Cognitive Scores at Different Time Points: Before Treatment and at Four, Eight, and Twelve Weeks of Treatment

T0: Before treatment, T1: At 4 weeks of treatment, T2: At 8 weeks of treatment, T3: At 12 weeks of treatment.

Calgary Depression Scale for Schizophrenia (CDSS)

The CDSS is an outcome measure rated by the clinician which is specified to evaluate the severity of depression in individuals with schizophrenia. CDSS differentiates between depressive symptoms in individuals with schizophrenia, as well as negative and extrapyramidal symptoms in these patients. The validated Persian version of the CDSS was used in this study (21). This scale has a Cronbach's alpha of 0.86, test-retest reliability of 0.82, as well as high sensitivity (0.79) and specificity (0.84).

Since the presence of prominent depressive symptoms can mimic the negative symptoms of schizophrenia, we used the CDSS to exclude patients experiencing significant depressive symptoms.

Statistical Analyses

Data analysis was done using the IBM SPSS statistic software, version 25. P-values of lower that 0.05 were considered statistically significant when interpreting the results. We used an intention-to-treat approach as all included patients received the medication (or placebo according to their treatment allocation), and completed the intended treatment course. They all were included in the analyses.

Positive and negative scores from PANSS scale and cognitive evaluation scores from MoCA were compared between the two groups at T0, T1, T2, and T3 using a repeated measures Multivariate Analysis of Variance (MANOVA), with Time as a within-subject factor. The aim was to determine if there are significant differences between participants' scores at different time points of evaluation (T0, T1, T2, and T3). Pillai`s Trace MANOVA tests were applied for this purpose. Prior to the MANOVA, we evaluated the normality of distribution of each group's independent variables using Shapiro-Wilk test, all of which resulted in $p > 0.05$ (i.e., the data have normal distribution). Other assumptions of MANOVA were also met.

Ethical Considerations

The study is a double-blind randomized clinical trial which is approved by the national ethics committee (Approval No: IR.USWR.REC.1400.082). The protocol of this study was submitted to the Iranian registry of Randomized Clinical Trial (IRCTID: IRCT20210428051118N1). All participants or their authorized representatives provided written informed consent for their voluntary involvement in this study. The participants were informed about the confidentiality

and anonymity regarding the information collected in the study.

Results

Demographic data of patients in both groups are represented in Table 1. No significant differences were seen between the treatment and control groups regarding gender, education level and age. At the baseline evaluations, no difference was seen between the two groups in the level of group B vitamins (P = 0.47). However, the treatment group showed a higher level of group B vitamins at T3 (P = 0.04). Vitamin B levels are shown in Table 2. Treatment with group B vitamins were well tolerated by the patients and no adverse effect was reported during the study.

Table 1. Demographic Data of Patients of the Two Groups (Treatment and Placebo)

	Treatment Group	Control Group	P value
Gender (n)			
Female	13	14	0.71
male	12	11	
Education			
Primary - secondary school	2	3	
Pre-college	10	8	0.42
College	8	9	
University	5	5	
Age (years)			
< 30	0	0	
30-50	10	11	0.97
50-70	15	14	

Table 2. Values of Serum Vitamin B Levels Before Treatment and at Twelve Weekes of Treatment in the Two Groups (Treatment and Placebo)

	Treatment (N = 25), Mean ng/ml(SD)	Placebo (N = 25), Mean ng/ml(SD)	P-value
T0	17.6(5.3)	16.9(5.2)	0.47
T3	24.1(4.0)	17.7(5.1)	0.04

T0: Before treatment, T3: At 12 weeks of treatment.

The Scores of MoCA

The comparison of MoCA scores in both study groups in baseline and three follow-up sessions showed no significant differences (P > 0.05). The repeated measures MANOVA, assuming equal variance in the two groups, presented an increase in MoCA scores in both groups from T0 to T3; however, there was no significant MANOVA effect, Pillai's trace = 0.87 (F (4, 45) = 523.4, P = 0.12). Figure 4 demonstrates changes of the scores of MoCA in patients from baseline to twelve weeks of treatment. See tables 3 and 4 for details of scores.

Table 3. Results of Repeated Measures Multivariate Analyses of Variance (MANOVA) on Positive, Negative and Cognitive Scores of Patients in both Groups

Pillai`s Trace	Value	F(4, 45)	P-value	ηp^2
Positive symptoms	0.933	686.5	0.071	0.933
Negative symptoms	0.974	517.46	< 0.001	0.974
MoCA scores	0.875	523.407	0.121	0.875

ηp2: Partial eta squared

Schizophrenia Positive Symptoms

Comparing positive symptoms in both study groups in baseline and three follow-up sessions did not result in any significant differences (P > 0.05). The repeated measures MANOVA, assuming equal variance in both groups, showed a decreasing pattern in positive symptoms in both groups from T0 to T3; however, there was no significant MANOVA effect, Pillai's trace = 0.933 (F (4, 45) = 686.5, P = 0.071). Figure 2 demonstrates changes of the scores of positive

symptoms from baseline to twelve weeks of treatment. See Tables 3 and 4 for details of scores.

Table 4. Changes in Scores of Positive and Negative Symptoms, and MoCA Scores from Baseline to 12 Weeks of Treatment in both Groups of the Study (Treatment and Placebo)

	Group	T0	T3
Positive symptoms	Treatment Mean (SD)	19.96 (3)	19.76 (2)
	Placebo Mean (SD)	19.97 (3)	14.74 (2)
Negative symptoms	Treatment Mean (SD)	29.96 (4)	16.06 (4)
	Placebo Mean (SD)	21.95 (4)	24.87 (3)
MoCA scores	Treatment Mean (SD)	18.38 (3)	19.51 (3)
	Placebo Mean (SD)	22.42 (3)	14.47 (3)

T0: Before treatment, T3: At 12 weeks of treatment, MoCA: Montreal Cognitive Assessment

Schizophrenia Negative Symptoms

The comparison of negative symptoms in both study groups in baseline and three follow-up sessions did not show any difference ($P > 0.05$) at T0, T1, and T2. However, a significant difference was observed between the two groups at T3 (lower negative symptoms score in the treatment group, $P = 0.043$). The repeated measures MANOVA, assuming equal variance in both groups, showed a statistically significant MANOVA effect; Pillai's trace = 0.974 ($F (4, 45) = 517.46$, $P < 0.001$). Figure 3 demonstrates changes of the scores of negative symptoms from baseline to twelve weeks of treatment. See Tables 3 and 4 for details of scores.

Discussion

In the present double-blind placebo-controlled randomized clinical trial, we examined the impact of group B vitamins as an adjuvant treatment in addition to second-generation antipsychotics in the management of schizophrenia. In our study, the effect of this treatment was evaluated on cognitive function, as well as on negative and positive symptoms in individuals with schizophrenia. We observed improvement in MoCA, positive and negative scores from T0 to T3 for both the treatment and control groups. However, only negative symptoms showed a significant improvement at T3 in the treatment group compared to the control group. We did not observe the differential impact of group B vitamins combination and placebo on positive and cognitive scores.

The impact of B vitamins on negative symptoms in the present study aligns with earlier findings on the effect on this adjuvant treatment on different symptoms of patients with schizophrenia (see for example the work by Firth and colleagues (3)). Our results regarding positive symptoms and cognitive functions are aligned with those presented by Allott and colleagues (16). It is important to highlight that Allott *et al*. examined how group B vitamins influence symptoms in individuals experiencing their first episode of psychosis. They indicated that a 12-week supplementation of B vitamins might not enhance general psychopathology and overall neurocognitive performance, but it could result in particular neuroprotective effects related to attention and vigilance (16).

The absence of difference between the treatment and control groups regarding positive symptoms and cognitive abilities could be attributed to different factors, namely the dosage, combination and duration of the treatment as well as the sample size of the study. Particularly, compared to published works, in our study the adjuvant treatment included a 12-week administration of a combination of relatively low doses of vitamin B1 (15mg), B2 (15mg), B6 (10mg), B12 (10µg) and nicotinamide (50 mg). However, previous studies have shown that higher doses of vitamin B12 (400micrgrams) on a large group of patients for a longer duration of treatment (16 weeks) in combination with folic acid improve negative symptoms of schizophrenia (14). Similarly, a long-term (24 weeks) administration of high-dose pyridoxamine add-on treatment (1200-2400 mg/day) on a small sample of patients has been shown to be effective for a specific group of individuals with schizophrenia who experienced increased carbonyl stress (22). The latter findings, however, should be viewed cautiously because of the relatively limited sample size.

A noteworthy difference between our study and previous works is the absence of folic acid in our vitamin B combination formula. A relatively large body of evidence support the effect of folate in improving symptoms of schizophrenia. Moreover, there is compelling evidence on the associations between low levels of folate deficiency and the occurrence and development of schizophrenia (15, 23). In our adjuvant treatment, we decided to include less studied subgroups of vitamin B and for this reason we did not include folic acid in the combination. This can also partly explain the absence of significant improvement in positive and cognitive symptoms.

Another explanation for the lack of beneficial effects of group B vitamins could be related to the chronicity of the disease. As reported by previous research works, the beneficial effects of group B vitamins on negative symptoms and cognitive functions are mainly observed when these supplements are administered early in the

course of the disease (3). However, few studies focusing on the first episode psychosis have shown improvement in attention and vigilance in these patients (16). In the present work, we recruited patients who were admitted at the center for chronic care and rehabilitation. This may influence the beneficial effects of vitamin B on these symptoms.

Several studies have indicated that polymorphism in genes related to the metabolism, absorption, and functionality of B vitamins are related to a higher risk of the development of psychiatric and cognitive disorders (24). A literature review by Brown and Roffman suggested that B12 and folate supplement adjuvant treatment has been effective on symptoms of schizophrenia (mainly negative symptoms) especially in patients with folate deficiencies. Such a response to this treatment was particularly affected by a genetic variant in FOLH1, which aids the absorption of dietary folates from the intestinal lumen (25). The effect of these polymorphisms was not implicated and analyzed in our study.

Limitation

We note that the present study has several limitations that encourage further investigation. We had a relatively low number of participants which could affect the observed power of the results, requiring cautious interpretation. Another limitation is the limited follow-up time period which may not be sufficient to observe significant differential effects of the treatment between the two groups and different subgroups of symptoms. Also, in our study, different B vitamins on the treatment of schizophrenia were not studied separately. Finally, it is worth noting that although all the participants took second generation antipsychotic treatments, not all of them were treated with the same medication. Taking into account the different pharmacological functions these medications and the limited number of participants in each group, this may result in inhomogeneous responses to the treatment and hinder any possible beneficial effects of vitamin B adjuvant treatments in schizophrenia.

Altogether the results and limitations of the present work encourage further studies which include a larger group of participants, longer follow-up duration, investigating the effect of disease duration, and investigating how each subgroup of vitamin B influences the symptoms. Considering that the beneficial impact of vitamin B on early stages of the disease, it would be valuable to perform further studies comparing the effects of vitamin B group in the management of individuals with recently diagnosed schizophrenia versus those with chronic schizophrenia.

Conclusion

The present work employed a combination of B vitamins – as an adjuvant treatment to antipsychotic medication – in the management of symptoms in individuals with schizophrenia. A decrease in negative symptoms was observed in the treatment group at 12 weeks following the beginning of treatment. No significant effects were seen on positive symptoms and cognitive functions. Further studies with higher doses of B vitamins, including patients in the earlier stages of the disease and a larger number of study population are recommended.

Acknowledgment

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Conflict of Interest

None.

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