Vitamin B_6 as Add-On Treatment in Chronic Schizophrenic and Schizoaffective Patients: A Double-Blind, Placebo-Controlled Study

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Background: Vitamin B_6, or pyridoxine, plays an intrinsic role in the synthesis of certain neurotransmitters that take part in development of psychotic states. Several reports indicate that vitamin B_6 may be a factor in a number of psychiatric disorders and related conditions, such as autism, Alzheimer's disease, hyperactivity, learning disability, anxiety disorder, and depression. Moreover, there are anecdotal reports of a reduction in psychotic symptoms after vitamin B_6 supplementation of psychopharmacologic treatment of patients suffering from schizophrenia or organic mental disorder. The aim of this study was to examine whether vitamin B_6 therapy influences psychotic symptoms in patients suffering from schizophrenia and schizoaffective disorder.

Method: The effects of the supplementation of vitamin B_6 to antipsychotic treatment on positive and negative symptoms in 15 schizophrenic and schizoaffective patients (DSM-IV criteria) were examined in a double-blind, placebo-controlled, crossover study spanning 9 weeks. All patients had stable psychopathology for at least 1 month before entry into the study and were maintained on treatment with their prestudy psychoactive and antiparkinsonian medications throughout the study. All patients were assessed using the Positive and Negative Syndrome Scale (PANSS) for schizophrenia on a weekly basis. Patients randomly received placebo or vitamin B_6, starting at 100 mg/day in the first week and increasing to 400 mg/day in the fourth week by 100-mg increments each week.

Results: PANSS scores revealed no differences between vitamin B_6- and placebo-treated patients in amelioration of their mental state.

Conclusion: Further studies with larger populations and shorter duration of illness are needed to clarify the question of the possible efficacy of vitamin B_6 in treatment of psychotic symptoms in schizophrenia.

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Knowledge of the function of vitamins in the human body has expanded rapidly in the last few decades. A deficiency of certain vitamins, especially the B-complex vitamins, can cause psychiatric symptoms. Vitamin B_6, i.e., pyridoxine, plays a basic role in the synthesis of certain neurotransmitters, including the biogenic amines (dopamine, serotonin, histamine, norepinephrine, and epinephrine) and γ-aminobutyric acid (GABA).[1,2] Low levels of vitamin B_6 have been reported in depressed patients.[3,4] Studies have been published that show vitamin B_6 to be effective in the treatment of a number of psychiatric disorders and related conditions, such as autism,[5] Alzheimer's disease,[6] hyperactivity and learning disability,[7] anxiety disorder,[8,9] and tardive dyskinesia.[10–12] The published studies examined the influence of high-dose, long-term treatment with various vitamins in combination with drug therapy or as monotherapy.[13] None of them examined vitamin B_6 specifically, and none focused on the effects of long-term augmentation of antipsychotic agents with high doses of viatmin B_6. There are some anecdotal reports of a reduction in psychotic symptoms after vitamin B_6 supplementation to treatment of patients suffering from schizophrenia or organic mental disorder.[10–12] We found only 3 reports[14–16] of studies of comparatively large groups of patients using vitamin B_6 supplementation to antipsychotic treatment of schizophrenic patients; unfortunately, the studies were not controlled, and no conclusive clinical trials have been undertaken. The purpose of this study was to examine whether vitamin B_6 influences psychotic symptoms in patients suffering from refractory schizophrenia and schizoaffective disorder, using an add-on design.

METHOD

Of 32 chronic schizophrenic and schizoaffective inpatients, 15 (4 men and 11 women) agreed to take part in this

Table 1. Demographic and Clinic Characteristics of Patients (N = 15)

Characteristic	Value
Gender, N, female/male	11/4
Age, y, mean ± SD (range)	50.0 ± 14.2 (28–71)
Smoking/nonsmoking, N	8/7
DSM-IV diagnosis, N	
Schizoaffective disorder	6
Paranoid schizophrenia	9
Duration of illness, y, mean ± SD (range)	18.6 ± 13.1 (2–42)
Duration of tardive dyskinesia, y, mean ± SD (range)	5.2 ± 4.2 (1–15)
Treatment, mean ± SD dosage[a] (range); N	
Haloperidol decanoate, mg/4 wk	133.7 ± 72.4 (100–200); N = 4
Fluphenazine decanoate, mg/4 wk	44.5 ± 19.9 (25–64); N = 2
Perphenazine	24 ± 9 (16–32); N = 3
Penfluridol, mg/wk	25 ± 7 (20–30); N = 2
Clozapine	275; N = 1
Risperidone	3; N = 1
Olanzapine	12.5 ± 5.0 (5–15); N = 4
Lithium	1350 ± 636 (900–1800); N = 2
Valproic acid	700 ± 424 (400–1000); N = 2
Carbamazepine	900; N = 1
Trihexyphenidyl	4.18 ± 1.66 (2–6); N = 7
Biperiden	3.96 ± 1.87 (2–6); N = 5

[a]All dosages shown in mg/day unless otherwise specified.

study. The mean ± SD age of the patients was 50.0 ± 14.2 years (range, 28–71 years). Nine of the patients met DSM-IV criteria for schizophrenia, and 6 met DSM-IV criteria for schizoaffective disorder. Ten of the patients had been ill for longer than 10 years and had been receiving neuroleptic drug therapy for a similar period. To avoid any influence of acute psychotic states and to monitor for response to the therapeutic influence of antipsychotic medications, we elected to study only chronic schizophrenic patients with stable resistant positive psychotic symptoms treated with maintenance psychopharmacotherapy. All patients had been hospitalized for long periods of time (from 1 to 3 years). The mental status and drug regimen of all patients were unchanged for at least 1 month before entry into the study. All of the subjects were taking neuroleptic medications. Patient characteristics are presented in Table 1. Informed written consent was obtained from all patients after they received detailed information about the study. The Helsinki Ethics Committee of the hospital approved the study.

At the start of the study, the patients were receiving a mean dose of 490 mg/day chlorpromazine equivalents, with a range of 200 to 750 mg/day (see Table 1). Six patients were treated with atypical neuroleptics: 4 received olanzapine (5–15 mg/day), 1 received clozapine (275 mg/day), and another received risperidone (3 mg/day). Twelve patients were concurrently receiving anticholinergic-antiparkinsonian agents (biperiden or trihexyphenidyl). Five patients were treated with mood stabilizers: 1 patient received carbamazepine (900 mg/day), 2 patients received lithium (900–1800 mg/day), and another 2 patients received valproic acid (400–1000 mg/day).

The study design was double blind and placebo controlled and included a randomized crossover of two 4-week treatment periods with either vitamin B_6 or placebo. Throughout the study, all psychotropic drugs were maintained at fixed dosages. Vitamin B_6 or placebo was administered in doses increasing from 100 mg/day in the first week to 400 mg/day in the fourth week by 100-mg increments each week. Following a 1-week washout period, all subjects were crossed over to the alternate treatment for another 4 weeks. As of the second week of each study arm, the medications were administered in twice-daily divided doses.

All patients were assessed by the same (blinded) investigators (V.L., C.M., A.K., U.L.), using the Positive and Negative Syndrome Scale (PANSS)[17] for schizophrenia and the Clinical Global Impressions scale (CGI) for psychosis.[18] Patients were assessed at baseline and then weekly, prior to and after crossover. All study and routine medications were taken by the participants in the presence of nursing staff for purposes of monitoring and improved compliance.

In addition to the clinical assessment of response, plasma levels of vitamin B_6 were evaluated in all patients at baseline and every 2 weeks. The plasma levels of vitamin B_6 were not reported to the raters in order to keep them "blind" to the patients' drug assignment. Plasma levels of vitamin B_6 were determined by radioenzymatic assay for direct measurement of plasma pyridoxal 5'-phosphate (PP). This assay is specific for the active form of vitamin B_6 only. The normal range of plasma PP concentration according to this analysis is 2 to 120 nmol/L.[19] All patients were maintained on the regular, balanced hospital diet.

Statistical Analysis

Placebo-drug differences were examined with repeated-measures analysis of variance (ANOVA) for 2-period crossover design as described by Fleiss.[20]

RESULTS

Vitamin B_6 was well tolerated by all patients, and all patients were able to receive the maximal dose of 400 mg/day with no adverse effects.

PANSS scores revealed no differences between the 2 groups at baseline. Repeated-measures ANOVA for the 2-period crossover design also revealed no significant differences ($p > .05$) between vitamin B_6 and placebo treatment with respect to the endpoint mean scores on the PANSS (Table 2). There were no significant correlations between PP level and PANSS scores ($R = 0.2$ for the negative symptom subscale and $R = 0.1$ for the positive symptom subscale).

Table 2. Positive and Negative Syndrome Scale (PANSS) for Schizophrenia Subscale Ratings of 15 Patients Before and During Treatment With Vitamin B_6 and Placebo[a]

	Period I[b]				Period II[b]					Statistical Comparison[c]			
Outcome Measure	Baseline B(I)	Visit 1 (100 mg/d) T1	Visit 2 (200 mg/d) T2	Visit 3 (300 mg/d) T3	Visit 4 (400 mg/d) T4	Baseline II B(II)	Visit 6 (100 mg/d) T6	Visit 7 (200 mg/d) T7	Visit 8 (300 mg/d) T8	Visit 9 (400 mg/d) T9	Sources	F	df	p Value
Negative symptoms											T	0.09	1,13	< .8
											P	0.13	4,52	< .7
Vp (N = 8)	13.5 (4.8)	13.8 (4.7)	13.8 (5.3)	13.8 (4.3)	13.5 (4.6)	13.7 (4.7)	13.5 (4.4)	13.6 (3.9)	12.6 (4.8)	13.3 (5.0)	V	0.72	1,13	< .6
											T × P	1.72	1,13	< .2
Pv (N = 7)	14.6 (4.7)	13.8 (4.9)	14.1 (5.1)	13.4 (4.1)	14.3 (5.0)	14.3 (5.1)	14.4 (5.0)	14.7 (5.4)	14.0 (4.9)	14.4 (5.3)	T × V	1.1	4,52	< .4
											P × V	1.3	4,52	< .3
											T × P × V	0.5	4,52	< .7
Positive symptoms											T	0.44	1,13	< .5
											P	0.2	1,13	< .7
Vp (N = 8)	14.1 (2.8)	14.4 (2.7)	14.4 (3.7)	14.6 (3.1)	14.4 (3.1)	14.5 (3.3)	14.5 (3.2)	14.0 (3.5)	14.3 (3.7)	14.4 (3.5)	V	0.19	4,52	< .9
											T × P	0.75	1,13	< .4
Pv (N = 7)	15.6 (3.6)	15.3 (3.3)	15.6 (3.3)	14.7 (3.1)	15.5 (3.3)	15.3 (3.3)	15.4 (3.1)	14.0 (3.2)	15.6 (3.2)	15.6 (3.1)	T × V	1.02	1,13	< .4
											P × V	0.4	4,52	< .9
											T × P × V	1.8	4,52	< .3
Plasma pyridoxal 5'-phosphate level (nmol/L)											T	2.94	1,13	< .1
											P	0.04	1,13	< .8
											V	54.72	4,52	< .000
Vp (N = 8)	49.3 (17.1)	307.4 (87.9)*	458	(131.7)*	303.3 (63.1)*	689.6 (75)*	56.4 (48.6)†	115 (150.5)†	77.3 (97.0)†	88.5 (175.1)†	108.8 (173)†	T × P	228.9	1,13	< .000
												T × V	15.5	4,52	< .000
Pv (N = 7)	40.6 (26.9)**	54.6 (17.6)**	54.4 (28.7)**	42.8 (18.3)**	52.6 (14.7)**	43.7 (5.7)**	459 (102.5)‡	340.6 (61)‡	478.8 (42.6)‡	453.5 (113)‡	P × V	16.8	4,52	< .000
											T × P × V	51.7	4,52	< .000

[a]Abbreviations: B = baseline, P = period, Pv = placebo followed by vitamin, T = treatment, V = visit, Vp = vitamin followed by placebo. A 1-week washout period followed period I and preceded period II. [b]Values shown as mean (SD). [c]Three-way fixed-effects repeated-measure analysis of variance; between-group comparison for placebo vs. vitamin B_6; within-group comparisons for periods (period I vs. period II) and visits (baseline and visits 1–4 and baseline II and visits 6–9). *p < .001 vs. B(I), †p < .001 vs. Vp(T4), ‡p < .001 vs. Pv(B[II]),**p < .001 vs. Pv(T6); Scheffe post hoc test.

The CGI revealed no significant improvement for either group. Only 5 patients showed improvement (1 marked, 1 moderate, and 3 mild). The others were unchanged or fared worse (Table 3).

Plasma PP levels at baseline were within the normal range in 10 patients (20–120 nmol/L). In 1 patient, an increased PP level was found (163.5 nmol/L), and in 4 patients, the PP level was low (5.0–16.2 nmol/L). Levels of vitamin B_6 were significantly higher after the second week of the treatment period (mean ± SD = 389 ± 55.2 nmol/L) than at baseline (49.0 ± 6.8 nmol/L) or after placebo administration (57.4 ± 15.4 nmol/L) ($p < .001$).

DISCUSSION

Both the pathogenesis of schizophrenia and the precise mode of action of the various antipsychotics found to be clinically effective in the treatment of the disorder are unclear to date.

The idea of using vitamins to treat schizophrenia was based on the theoretical assumption that the illness was related to a biological imbalance, which could be corrected by the addition of vitamins.[21] Vitamin B_6 consists of several related biologically active compounds (pyridoxine, pyridoxal, and pyridoxamine), which are metabolized in the body to their respective phosphates. All 6 biologically active forms of vitamin B_6 can be converted into each other. In humans, vitamin B_6 is transported into the central nervous system by the cerebrospinal fluid.[22,23] Vitamin B_6 is involved in crucial steps of the synthesis of several neurotransmitters. In the nervous system, pyridoxine-dependent enzymes fall into 2 major categories: transaminases and L-amino acid decarboxylases. Vitamin B_6 in the form of pyridoxal phosphate has an important coenzyme function in the enzymatic decarboxylation of 3,4-dihydroxyphenylalanine (dopa) to dopamine, in the conversion of tryptophan to both nicotinic acid and serotonin, and in the conversion of glutamic acid to GABA.[13,24]

The interactions between the various neurotransmitters are myriad, and disorders in these interactions appear to be related to psychotic conditions. Hypotheses to explain the pathophysiology of schizophrenia include changes in dopamine, serotonin, nor-

Table 3. Clinical Global Impressions Scale (CGI) Efficacy Index (total N = 15 patients)[a]

Therapeutic Effect	N
Marked: Vast improvement; complete or nearly complete remission of all symptoms	1
Moderate: Decided improvement; partial remission of symptoms	1
Minimal: Slight improvement, which does not alter status of care of patient	3
Unchanged or worse	10

[a]No patient developed side effects.

epinephrine and GABA metabolism and, based on these theories, it seems reasonable to suppose that vitamin B_6 may influence psychotic symptoms.

Several previous studies[10–12,14] report an improvement in psychotic symptoms in schizophrenic patients treated with vitamin B_6 in addition to their regular antipsychotic regimen. Bucci[14] first reported in 1973 on an improvement in psychotic symptoms in 8 of 15 chronic schizophrenic patients after 4 to 6 weeks of treatment with 150 mg/day of vitamin B_6. Sandyk and Pardeshi[10] in 1990 described a reduction of psychotic behavior following 7 to 14 days of therapy with only 100 mg/day of vitamin B_6. Ananth et al.[15] reported positive results following treatment with 75 mg/day of vitamin B_6 combined with 3000 mg/day of nicotinic acid in 30 schizophrenic patients. Lerner and Liberman[11] added 200 mg/day of vitamin B_6 to an antipsychotic regimen and observed an improvement of psychotic signs after 5 days. Lerner et al.[12] treated 5 chronic schizophrenic patients with 100 mg/day of vitamin B_6, 3 of whom showed significant improvement in psychotic symptoms after 3 weeks of the combined treatment. However, in the present double-blind controlled study, we found no evidence of a statistically significant therapeutic effect of vitamin B_6 on psychotic symptoms in a series of 15 patients suffering from resistant schizophrenia or schizoaffective disorder. Our present findings support the results of Ban et al.[16]

Based on those studies that described positive results of pyridoxine treatment as a part of a combination formula in schizophrenic patients, we decided in this study to examine more specifically its influence, as addition to regular antipsychotic treatment, on psychotic symptoms.

The lack of an observable effect of vitamin B_6 may be related to the fact that schizophrenia is a heterogeneous disease, with different responses to various treatments depending on age variations, illness duration, and length of treatment. Such variables may underlie the contradictory results between studies. Our sample contained a small number of chronic psychotic schizophrenic patients with minimal improvement on treatment with classical and atypical neuroleptics. Sample variables could be the reason for lack of efficacy of pyridoxine as add-on therapy, which contradicts previous positive results. Furthermore, vitamin supplementation can sometimes take up to a few months to achieve positive influence. For example, Godfrey et al.[25] conducted a 6-month double-blind, placebo-controlled trial with methylfolate in 41 patients with acute psychiatric disorders who had borderline or definite folate deficiency. These authors reported significant improvement among both depressed and schizophrenic patients who were treated with folic acid. Differences in outcome scores between methylfolate and placebo groups became greater with time. Our study lasted only 1 month, and the negative findings obtained in our study may be explained by its short duration.

The possible limitations of our study are as follows: First, the study group is small (as in other studies), and the investigation should be reproduced in larger patient populations to prevent type II error. The differences in PANSS scores between groups were far from being statistically significant (negative symptoms: $p = .80$, and positive symptoms: $p = .50$). Based on a formal power calculation, a sample size of 90 pairs would have been needed to find the obtained differences as significant. Of course, even a significant difference alone is generally not sufficient, as one would want to see a sizable improvement on the PANSS—for example, 20%—to be clinically meaningful.

In addition, the study was short, and even in light of the fact that all other published studies showed improvement of mental symptoms within about a month, a longer trial period would possibly give clearer results.

Further studies with larger populations, shorter duration of illness, more uniform inclusion criteria, and longer period of vitamin B_6 supplementation are needed to clarify the question of the possible efficacy of vitamin B_6 in treatment of psychotic symptoms in schizophrenia.

Drug names: biperiden (Akineton), carbamazepine (Tegretol and others), chlorpromazine (Thorazine and others), clozapine (Clozaril and others), haloperidol (Haldol and others), olanzapine (Zyprexa), perphenazine (Trilafon and others), risperidone (Risperdal), trihexyphenidyl (Artane and others), valproic acid (Depakene).

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