Vitamin B_6 Treatment for Tardive Dyskinesia: A Randomized, Double-Blind, Placebo-Controlled, Crossover Study

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Background: Tardive dyskinesia (TD) is a significant clinical problem. Vitamin B_6 is a potent antioxidant and takes part in almost all of the possible mechanisms that are suggested as being associated with appearance of TD. The aims of this study were (1) to reexamine the efficacy and safety of higher doses of vitamin B_6 versus placebo in a greater sample of patients for a longer time and (2) to evaluate the carryover effect of vitamin B_6.

Method: A 26-week, double-blind, placebo-controlled trial was conducted in a university-based research clinic from August 2002 to January 2005 on 50 inpatients with DSM-IV diagnoses of schizophrenia or schizoaffective disorder and TD. In a double-blind crossover paradigm, all study subjects were randomly assigned to start treatment with either vitamin B_6 (daily dose of 1200 mg) or placebo. After 12 weeks of treatment and then a 2-week washout, subjects were crossed over to receive the other treatment for 12 weeks. The primary outcome measure was the change from baseline in Extrapyramidal Symptom Rating Scale (ESRS) scores.

Results: The mean decrease in ESRS clinical global impression scores from baseline to endpoint was 2.4 points in patients treated with vitamin B_6 and 0.2 points in patients treated with placebo ($p < .0001$). The mean decrease in the parkinsonism subscale score was 18.5 points and 1.4 points, respectively ($p < .00001$), and the mean decrease in the dyskinesia subscale score was 5.2 points and –0.8 points, respectively ($p < .0001$).

Conclusion: Vitamin B_6 appears to be effective in reducing symptoms of TD. The specific mechanisms by which vitamin B_6 attenuates symptoms of TD are not clear.

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Tardive dyskinesia (TD) is a common adverse effect generally caused by chronic use of classic neuroleptics. The prevalence of TD among subjects treated with classic neuroleptics for more than 1 year ranges from 3% to as high as 70% (depending on the diagnostic criteria and methodology).[1–3] The annual incidence in younger adults is 4% to 5%.[1,4] Cases of TD are often persistent, many are irreversible, and they may result in social and physiologic impairment.

Although second-generation agents have a significantly reduced potential for causing acute and tardive extrapyramidal symptoms,[5–7] each of them may also induce delayed movement disturbances.[8–17] Furthermore, despite the extensive use of second-generation agents in the majority of Western countries, most patients in third-world countries and up to half in Europe are still treated with typical antipsychotics; therefore, it is not surprising that TD remains a significant clinical problem.[18–21]

A large number of different medications have been studied in the treatment of patients with TD, but its management remains a significant problem for patients and a therapeutic conundrum for physicians.[22]

Some researchers have observed motor disturbances in vitamin B_6–deficient animals.[23,24] Preliminary evidence in human beings, published as several case reports,[25–30] open-label trials,[31,32] and randomized, double-blind, placebo-controlled trials,[33–35] demonstrates efficacy of

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vitamin B_6 in the treatment of TD and other drug-induced involuntary movement disorders.

In our previous study,[34] we evaluated the efficacy of the addition of vitamin B_6 (up to 400 mg/day) compared with placebo in treatment of TD and found it effective. Looking for new treatment options for TD and other long-term extrapyramidal symptoms, we decided to reproduce the study and reexamine the efficacy and safety of higher doses of vitamin B_6 versus placebo in a greater sample of patients and for a longer period.

Since our clinical impression was that the positive effect of vitamin B_6 on TD continued for a long period after treatment with the high dose of the medication (1200 mg/day) was stopped, a further purpose of this study was to evaluate the carryover effect of vitamin B_6.

METHOD

Subjects

From August 2002 to January 2005, we screened 67 schizophrenic and schizoaffective patients suffering from TD who were hospitalized in the Be'er Sheva Mental Health Center (Be'er Sheva, Israel).

All subjects were inpatients who fulfilled the following inclusion criteria: (1) DSM-IV diagnosis of schizophrenia or schizoaffective disorder; (2) a diagnosis of TD (according to DSM-IV-TR research criteria[36]), confirmed independently by 3 specialized psychiatrists well experienced in the diagnosis and treatment of movement disorders; (3) each of the psychotropic drug–induced movement symptoms should be of at least moderate severity, as measured by the clinical global impression (CGI) subscale of the Extrapyramidal Symptom Rating Scale (ESRS)[37,38]; (4) signs and symptoms of TD developed during exposure to a neuroleptic medication, within 4 weeks of withdrawal from oral neuroleptics, or within 8 weeks of withdrawal from a depot form; (5) exposure to psychotropic medication for at least 3 months prior to the appearance of the movement disorders; (6) duration of symptoms of at least 1 year; and (7) a stable psychotropic regimen for at least 1 month prior to entry into the study.

Complete medical and neurologic examinations, including laboratory tests, were performed before trial inclusion. Patients with a concurrent medical or neurologic illness that may have caused a state resembling any kind of tardive movement disorder and pregnant or lactating women were excluded from this trial. Patients who received any kind of vitamin supplementation were also excluded from the study, as were patients with evidence of substance or alcohol abuse.

The sample size was determined on the basis of the earlier studies[34,39] conducted in schizophrenic and schizoaffective patients suffering from TD. Of 67 screened subjects, 10 patients were discharged from the hospital before initiation of the study, and 7 more refused to take part in it. Thus, 50 patients (28 men and 22 women) with a mean ± SD age of 47 ± 11 years (range, 20–66 years) were eligible and included in the study. Thirty-four of the patients suffered from chronic schizophrenia, and 16 suffered from schizoaffective disorder. All patients had been hospitalized for 1 to 3 years. Most of them were smokers and had suffered from TD for less than 5 years. All patients were on a regular balanced hospital diet under the supervision of a clinical dietician and had no clinically relevant symptoms of malnutrition. The patients' characteristics are presented in Table 1.

Table 1. Demographic Data and Clinical Characteristics of the Patients

Characteristic	Whole Sample (N = 50)	Randomization[a]	
		Vitamin B_6 (N = 28)	Placebo (N = 22)
Gender, N			
Female	22	12	10
Male	28	16	12
Age, y			
Mean ± SD	46.8 ± 11.1	45.4 ± 12.3	48.5 ± 9.4
Range	20–66	20–62	29–66
Smoking status, N			
Smokers	46	26	20
Nonsmokers	4	2	2
DSM-IV diagnosis, N			
Schizophrenia	34	18	16
Schizoaffective disorder	16	10	6
Duration of illness, y			
Mean ± SD	19.0 ± 10.9	18.6 ± 10.0	19.5 ± 9.2
Range	2–41	2–41	4–34
Duration of tardive dyskinesia, N			
< 3 y	28	16 (57%)	12 (54%)
3–5 y	10	5 (18%)	5 (23%)
> 5 y	12	7 (25%)	5 (23%)
Treatment, N			
Typical antipsychotics	31	16 (57%)	15 (68%)
Atypical antipsychotics	19	10 (36%)	9 (41%)
Mood stabilizers	18	11 (39%)	7 (32%)
Anticholinergic agents	25	13 (46%)	12 (54%)

[a]There were no significant differences between the randomization groups.

The patients' psychotropic medication regimens remained unchanged throughout the study. Thirty-one patients received conventional psychotropics. The mean dose of current antipsychotic medications was 396.7 ± 280.4 mg/day in chlorpromazine equivalents (range, 150–1500 mg/day). Nineteen patients received atypical antipsychotics (9 patients: olanzapine 10–30 mg/day, mean 19.0 ± 8.4 mg/day; 4 patients: clozapine 100–400 mg/day, mean 275.0 ± 125.8 mg/day; 2 patients: risperidone 3–7 mg/day, mean 5.0 ± 2.8 mg/day; 2 patients: amisulpride 600 mg/day [each subject]; 1 patient: quetiapine 200 mg/day; 1 patient: ziprasidone 200 mg/day). Two patients were treated with a neuroleptic combination: 1 patient with a typical-atypical combination and another with an atypical-atypical combination. Eighteen patients received different mood stabilizers (lithium,

carbamazepine, or valproate) in combination with antipsychotic agents. Twenty-five patients were treated with anticholinergic agents for a long time prior to entering the study, with no dose changes during the trial. None of the patients were treated with β-blocker medications.

Procedure and Outcome Measures

After baseline assessment, subjects were randomly assigned to treatment: each patient was given either 2 tablets (300 mg each) of vitamin B_6 twice a day (1200 mg/day) or 2 tablets of placebo twice a day. The tablets were administered at 8 a.m. and 8 p.m. every day for 12 weeks (phase 1). After a 2-week washout period (following vitamin or placebo treatment), the patients were treated for the next 12 weeks with the other preparation (phase 2). Vitamin B_6 or placebo was given in addition to each patient's regular antipsychotic medication. A crossover design was chosen as an appropriate design for chronic patients in a stable pathologic condition, in an attempt to reduce variance and increase effective sample size.

Clinical Ratings

The ESRS was chosen to assess the severity of movement disorders. The ESRS was developed by Chouinard and Ross-Chouinard for epidemiologic studies of TD in schizophrenic patients chronically treated with various antipsychotic agents. It was also designed to rate 4 types of drug-induced movement disorders (both acute and delayed-onset): parkinsonism, akathisia, dystonia, and TD. Its sensitivity and validity were established through several clinical trials.[37,38] The parkinsonism subscale includes the assessment of core parkinsonian symptoms (expressive automatic movements, bradykinesia, rigidity, gait and posture, sialorrhea, and postural stability), as well as the assessment of tremor and akathisia. Each variable in this scale can be scored from normal (0) to extremely severe (6) according to the symptoms' severity. In addition, the ESRS also includes 3 assessments of clinical global impression: parkinsonism, dystonia, and dyskinesia.

The safety and tolerability of high-dose vitamin B_6 were evaluated by assessing the incidence and severity of adverse events for all patients who had received at least 1 dose of study medication during that phase, as well as the withdrawals due to adverse events.

All patients were assessed by the same investigators (V.L., A.K., I.L.), who had undergone pretrial training in the assessment tool. The interrater correlation coefficient (κ) for the parkinsonism subscale was 0.92 and for the dyskinetic movement subscale and CGI was 0.89. The assessment was performed at baseline and at weeks 2, 4, 8, 12 (end of phase 1), 14 (end of washout period), 16, 18, 22, and 26 (end of phase 2). All assessments were made in the morning at the same time of day (10 a.m. ± 1 hour) in order to rule out any influence of diurnal fluctuation of the TD symptoms.[40] All study and routine medications were taken by the participants in the presence of nursing staff. This careful monitoring ensured compliance.

A 20% reduction in ESRS scores from baseline to week 12 on the rating scales was taken to represent no response; 21% to 40%, minimal improvement; 41% to 60%, moderate improvement; and more than 61%, marked improvement.[34]

In addition to the clinical measurements, blood samples for assessment of plasma vitamin B_6 levels were obtained at baselines (phases 1 and 2) and at the end of study weeks 12 and 26. Blood (5 mL) was drawn before breakfast and first daily medication administration; it was immediately centrifuged for 10 min at room temperature and 3000 rpm, and the supernatant was frozen at –18°C until analyzed. All blood samples were drawn in light-proof test tubes, and frozen serum was also kept in the same conditions until analyzed. Measurement of the physiologically active vitamer of vitamin B_6, pyridoxal-5′-phosphate (PLP), was performed by high-performance liquid chromatography (HPLC) separation according to the method of Botticher and Botticher.[41] The normal level of plasma PLP concentration according to this analysis is more than 20 nmol/L. The plasma levels of vitamin B_6 were not reported to the raters, in order to keep them "blind" to the patient's drug assignment.

The research protocol was approved by the Institutional Review Board of Soroka Medical Center (Be'er Sheva, Israel). Written informed consent was obtained from all participants following a detailed explanation of the nature of the study.

Statistical Analysis

All statistical analyses were performed using Statistica 7 for Windows.[42] Differences between groups in the demographic and baseline clinical data were compared with the Pearson χ^2 test, and baseline scores were analyzed with the Student t test. All subjects were exposed to both vitamin B_6 and placebo in separate study phases. To compare the effects of treatment in groups (at 5 visits during vitamin B_6 treatment vs. 5 visits during placebo treatment), the data were organized for 2-phase crossover design,[43] and analysis of variance of the ESRS subscales was performed. For dependent variables, 5 time points were used as within effect. Treatment (vitamin B_6/placebo) and treatment order (for evaluating carryover effect) were used as independent factors, and analysis for specific effects and interactions was performed. In the case of positive interactions, a post hoc least significant difference (LSD) test was performed. Analyses of changes in ESRS for the parkinsonism, dyskinetic, and CGI subscales separately by analysis of variance (ANOVA) with repeated measures were done in the same way, with changes

Table 2. Efficacy of Vitamin B_6 (N = 23) Versus Placebo (N = 22) in Schizophrenic Patients With Tardive Dyskinesia in Phase I (ESRS subscales analysis, mean ± SEM, N = 45)

	Score					Treatment Effect[b]		Time[c]		Time × Treatment Interaction[c]	
ESRS Subscale	Baseline[a]	Week 2	Week 4	Week 8	Week 12	F	p	F	p	F	p
Parkinsonism						10.7	< .002	24.6	< .00001	13.1	< .00001
Vitamin	28.3 ± 2.1	18.0 ± 2.5	14.1 ± 2.4	11.6 ± 2.1	9.8 ± 2.0[d]						
Placebo	26.8 ± 2.2	25.5 ± 2.6	24.4 ± 2.4	23.9 ± 2.2	25.4 ± 2.1						
CGI of parkinsonism						12.0	< .001	21.9	< .0001	7.8	< .00001
Vitamin	5.3 ± 0.4	4.1 ± 0.4[d]	3.3 ± 0.4[e]	2.7 ± 0.4[e]	2.4 ± 0.4[e]						
Placebo	5.5 ± 0.3	5.3 ± 0.3	4.9 ± 0.4	4.7 ± 0.4	5.0 ± 0.3						
Tardive dyskinesia						0.09	.760	3.6	< .0002	6.3	< .00009
Vitamin	9.9 ± 1.5	7.6 ± 1.3	6.4 ± 1.1	5.3 ± 1.2	4.7 ± 0.9						
Placebo	6.6 ± 1.5	7.4 ± 1.2	7.7 ± 1.3	7.2 ± 1.4	7.4 ± 1.3						
CGI of tardive dyskinesia						0.5	.48	10.0	< .0001	6.9	< .00003
Vitamin	4.4 ± 0.5	3.7 ± 0.5	3.1 ± 0.4	2.4 ± 0.5	2.1 ± 0.4[d]						
Placebo	3.5 ± 0.5	3.9 ± 0.5	3.8 ± 0.5	3.4 ± 0.5	3.4 ± 0.5						
Overall CGI						13.3	< .0001	29.5	< .0001	20.1	< .0001
Vitamin	4.3 ± 0.2	3.5 ± 0.2	3.0 ± 0.2	2.3 ± 0.2[d]	1.9 ± 0.2[e]						
Placebo	4.1 ± 0.2	4.0 ± 0.2	4.0 ± 0.2	3.9 ± 0.3	3.9 ± 0.2						

[a]No difference between groups at baseline; p > .05.
[b]df = 1,43.
[c]df = 4,172.
[d]Least significant difference (LSD) post hoc test p < .025.
[e]LSD post hoc test p < .01.
Abbreviations: CGI = Clinical Global Impression, ESRS = Extrapyramidal Symptom Rating Scale, SEM = standard error of the mean.

from baseline to endpoint used as dependent variables for phase 1.

RESULTS

After breaking the code following database lock, it was found that 28 patients (16 men and 12 women; mean age = 45.4 ± 12.3 years) began treatment with vitamin B_6, and 22 patients (12 men and 10 women; mean age = 48.5 ± 9.4 years) received placebo. No significant demographic or clinical differences were found between the vitamin B_6 and placebo groups (Table 1).

Vitamin B_6 was well tolerated by most of the patients, and they were able to receive the maximal dose of 1200 mg/day during the whole study. Only 1 patient experienced acne during the vitamin phase, and another developed an allergic reaction (light itch) after a 2-month treatment. Of 50 randomized patients, 5 subjects did not comply with the treatment regimen after the first month of treatment since they did not want to add 4 more pills, and therefore they were excluded from the statistical analysis. Of the 45 patients who completed phase 1, 9 patients (5 taking vitamin and 4 taking placebo) dropped out before completing the first rating of the second phase after crossover (1 patient due to acne and 1 due to allergic reaction, both in spite of TD improvement, and 7 patients due to noncompliance). Thus, 36 patients completed both phases of the study. None of the patients had dystonia or akathisia.

We did not find any correlation between age, duration of illness, and duration of TD and baseline ESRS scores. The 2-way ANOVA of phase 1 completers (45 patients) is shown in Table 2. The baseline scores of the parkinsonism, dyskinetic movements, and CGI subscales did not reveal any significant difference between the vitamin and placebo groups.

A highly significant therapeutic effect of vitamin B_6 in the parkinsonism and dyskinetic subscales during phase 1 was found. CGI of severity of parkinsonism and TD reflected the same changes as in the appropriate subscales (Table 2).

Twenty-one (91%) of 23 patients who were treated with vitamin B_6 demonstrated different levels of clinical improvement: 8 patients (35%) showed marked improvement, 7 patients (30%) showed moderate improvement, and 6 patients (26%) showed minimal improvement. Only 2 patients (9%) showed no change. Among 22 patients who were treated with placebo, 3 patients (14%) demonstrated minimal improvement, 17 (77%) showed no effect, and the condition worsened in 2 patients (9%) ($\chi^2 = 29.7$, df = 3, p < .0001).

The results of the crossover phase are shown in Table 3. Thirty-six subjects (18 patients taking vitamin and 18 taking placebo) completed phase 2 (after washout period and crossover). Changes in ESRS scores also showed that vitamin B_6 was significantly more effective than placebo (Figures 1 and 2). A significant difference on the parkinsonism subscale demonstrated improvement beginning with the fourth week of vitamin B_6 treatment (LSD post hoc test for the fourth week, p < .004); on the dyskinetic subscale, the significant improvement appeared from the eighth week of treatment with vitamin B_6 (LSD post hoc test p < .01). CGI of severity of parkinsonism and TD showed the same changes as in the appropriate subscales (Table 3). The CGI subscale also showed a significant

Table 3. Efficacy of Vitamin B_6 Versus Placebo in Schizophrenic Patients With Tardive Dyskinesia Who Completed the Whole Crossover Study (ESRS subscales analysis, mean ± SEM, N = 36)

ESRS Subscale	Baseline[e] Score	Improvement (Δ from baseline)[a] Week 2	Week 4	Week 8	Week 12	Treatment Effect[b] F	p	Treatment × Time Interaction[c] F	p	Time × Treatment × Order Interaction[c,d] F	p
Parkinsonism						45.3	< .00001	25.0	< .00001	2.3	< .09
Vitamin	24.1 ± 1.8	5.6 ± 0.9	10.3 ± 1.2[f]	12.6 ± 1.3[f]	14.9 ± 1.5[f]						
Placebo	19.8 ± 2.0	–0.7 ± 1.1	–1.8 ± 1.5	–3.3 ± 1.8	–4.9 ± 1.8						
CGI of parkinsonism						31.0	< .00001	13.9	< .00001	2.5	.07
Vitamin	5.1 ± 0.2	1.1 ± 0.2[d]	1.9 ± 0.3[f]	2.4 ± 0.3[f]	2.6 ± 0.3[f]						
Placebo	4.1 ± 0.4	–0.2 ± 0.2	–0.3 ± 0.3	–0.4 ± 0.4	–0.5 ± 0.4						
Tardive dyskinesia						17.9	< .0001	8.7	< .0003	2.2	< .09
Vitamin	8.7 ± 1.1	1.4 ± 0.5	2.7 ± 0.7	3.8 ± 0.9[d]	4.2 ± 0.8[d]						
Placebo	5.9 ± 1.0	–1.3 ± 0.6	–2.1 ± 0.9	–2.9 ± 1.0	–2.9 ± 0.9						
CGI of tardive dyskinesia						25.6	< .00001	9.4	< .00001	6.8	< .001
Vitamin	3.8 ± 0.4	0.5 ± 0.2	1.2 ± 0.3[f]	1.6 ± 0.3[f]	1.9 ± 0.3[f]						
Placebo	3.0 ± 0.3	–0.4 ± 0.2	–0.7 ± 0.2	–0.6 ± 0.3	–0.8 ± 0.3						
Overall CGI						60.6	< .0001	26.5	< .0001	6.2	< .0001
Vitamin	4.0 ± 0.1	0.7 ± 0.1	1.2 ± 0.2[d]	1.7 ± 0.2[f]	2.0 ± 0.2[f]						
Placebo	3.2 ± 0.2	–0.8 ± 0.1	–0.3 ± 0.2	–0.5 ± 0.2	–0.6 ± 0.2						

[a]Positive numbers indicate improvement; negative numbers indicate worsening.
[b]df = 1,34.
[c]df = 3,102.
[d]Least significant difference (LSD) post hoc test p < .01.
[e]No difference between groups at baseline; p > .05.
[f]LSD post hoc test p < .005.
Abbreviations: CGI = Clinical Global Impression, ESRS = Extrapyramidal Symptom Rating Scale, SEM = standard error of the mean.

Figure 1. Changes in Extrapyramidal Symptom Rating Scale (ESRS) Parkinsonism Subscale During the Crossover Design Treatment (N = 36)

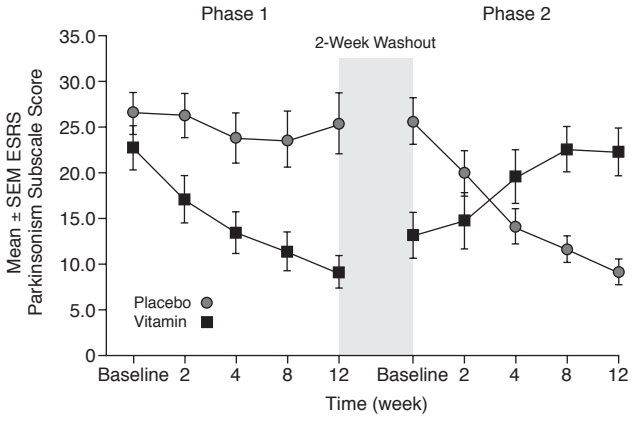
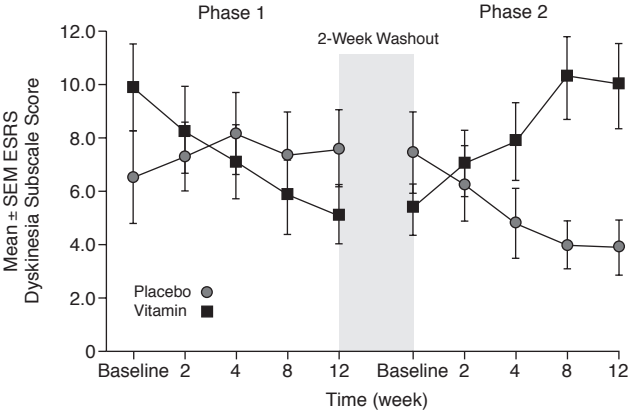


Figure 2. Changes in Extrapyramidal Symptom Rating Scale (ESRS) Tardive Dyskinesia Subscale During the Crossover Design Treatment (N = 36)



positive effect beginning with the fourth week of vitamin B_6 treatment (LSD post hoc test for fourth week, p < .004).

The carryover effect of vitamin B_6 in the parkinsonism and dyskinetic ESRS subscales was not significant (treatment-by-time-by-order interaction, p < .09); it was significant only in the CGI subscale (F = 6.2, df = 3,102; p < .0001). After a 2-week washout period, the patients with placebo substitution in the second phase showed no significant difference in CGI rates until the fourth week. Only after 6 weeks (2-week washout plus 4 weeks of placebo treatment) did the CGI scores return to pre–vitamin treatment state, and at the 12th week they nearly returned to the baseline level of ESRS scores.

Of 36 subjects who completed both phases of the study, 18 received vitamin treatment during phase 2 (after washout period and crossover). An overall beneficial effect was demonstrated in 14 patients (77%): 6 patients (33%) showed marked improvement (in 4 of them the movement disturbances completely disappeared), 4 patients (22%) had moderate improvement, and in 4 patients (22%) there was a minimal clinical improvement.

Another 4 patients (22%) remained without change. In the placebo group, only 1 patient (6%) demonstrated minimal improvement; all others were without change ($\chi^2 = 19.8$, df = 3, $p < .001$).

At the beginning of the study, the mean PLP level of the whole sample was under a lower limit of normal range (18.5 ± 19.7 nmol/L; range, 0.0–119.5 nmol/L), without statistical difference between the groups: 17.4 ± 23.8 nmol/L (range, 0.0–100.6 nmol/L) in the vitamin B_6 group and 19.8 ± 12.1 nmol/L (range, 1.9–119.5 nmol/L) in the placebo group ($p = .576$).

At the end of the first phase, the mean serum PLP level in the vitamin group was 351.4 ± 191.9 nmol/L (range, 40.5–698.9 nmol/L) and in the placebo group 37.5 ± 21.3 nmol/L (range, 9.8–103.0 nmol/L). We found no significant correlation between the serum PLP level and severity of TD at baseline evaluation or improvement in these symptoms after vitamin B_6 treatment ($r = –0.08$, $p = .6$). After a 2-week washout in the vitamin-treated patients, serum PLP levels diminished and the mean level was 39.5 ± 37.4 nmol/L (range, 6.5–119.5 nmol/L).

DISCUSSION

The results of this double-blind, placebo-controlled study suggest that a high dose of vitamin B_6 (1200 mg/day) is an effective and safe treatment for TD. Our findings demonstrated that the clinical effect was more impressive in improvement of the parkinsonian symptoms such as tremor and muscle rigidity. Although it was found that the large "effect size" in this study (Cohen d = 1.6) was the same as in our previous double-blind study[34] (Cohen d = 1.9), from the clinical point of view, the positive effect of vitamin B_6 in a high dose not only was seen during the treatment period, but continued for approximately 6 weeks after the medication was stopped in comparison to lower doses (400 mg/day). According to our previous study, this dose was also found to be effective, but for no longer than 1 week after ceasing its use. The present findings regarding a curative effect of vitamin B_6 are consistent with previous reports suggesting the beneficial influence of pyridoxine on movement disorders.[25–27,29–35] In some of them, high doses of pyridoxine were used (1000–1400 mg daily) and also caused an improvement of involuntary movements.[25,26,32,33,35]

To our knowledge, there have been several controversial reports about treatment of TD with vitamin B_6. Most of them were from uncontrolled studies, were from studies performed on a small group of patients, or were case reports without follow-up evaluation after termination of the add-on vitamin therapy.[25–31] Only 1 study was double-blind and placebo-controlled, but it was also performed on a relatively small sample (15 subjects).[34]

The decision to use high doses (1200 mg/day) of vitamin B_6 as treatment for TD was based on previous reports,[26,32,44,45] on our ongoing studies, and on the clinical practice follow-up lasting 3 years. The lack of a notable adverse effect of vitamin B_6, and reports about the safe use of high doses in children (average dose of 638.9 mg/day), justify application of such doses in adults.[46] Moreover, data published by some authors[44,47–49] support the assumption that pyridoxine is toxic in doses higher than 2 g per day.

We found no relationship between pretreatment serum PLP levels and clinical improvement. Therefore, we assume that serum PLP levels are not directly associated with TD and that serum concentration of PLP does not correlate directly with pyridoxine-dependent biological activity of amines.

Although there are various theories regarding the development of movement disorders, the pathophysiology is complex and remains to be fully elucidated.[50] There are 2 lines of speculation as to how vitamin B_6 may be involved in ameliorating TD, mainly through (1) dopamine, γ-aminobutyric acid, and serotonin and (2) scavenge of free radicals.[1,4,51–53]

From all of the information mentioned above, it is certain that vitamin B_6 has a part in almost all of the possible mechanisms associated with the development of TD. The pathophysiologic role of vitamin B_6, and its influence in alleviation of these symptoms, is complicated and still not adequately clear.

Our previous findings about the beneficial effect of vitamin B_6 in acute neuroleptic-induced akathisia[33,35] and lithium-induced tremor[32] may be an indication that the vitamin is effective in treatment of a broad spectrum of movement disorders.

Our study has a number of limitations, especially the fact that the study population is homogeneous and represents only inpatients, who may perhaps represent more severe and chronic schizophrenic subjects. We can make conclusions about vitamin B_6 effectiveness in other schizophrenic populations only by extrapolation of the results. Due to the relatively small sample, we could not divide the patients into subgroups related to the duration of TD. Such a division is recommended in order to evaluate the relationship between the effects of vitamin B_6 and length of the symptomatic period. For the same reason, we could not specify the groups in terms of typical versus atypical antipsychotic agents, which could be an indication or a clue for a possibly different mechanism of action. Another limitation is the lack of use of other assessment scales such as the Simpson-Angus Scale for tremor evaluation and the Barnes Akathisia Rating Scale, which could also be used for independent evaluation of these disturbances.

To date, there is no definitely accepted consensus treatment for this troublesome and intractable condition. The potential usefulness of vitamin B_6 in treating TD has clinical importance, since it has only rare and transitory side effects in relatively high doses.[54] In addition to our

encouraging results, further comparative studies of vitamin B_6 are necessary to prove its efficacy. In order to examine its long-term treatment effect, a longer study of vitamin B_6 application is needed. Our clinical observation, during more than 3 years of follow-up, revealed no side effects in patients who continued vitamin B_6 treatment at the studied dose.

Drug names: carbamazepine (Carbatrol, Equetro, and others), clozapine (Clozaril, FazaClo, and others), lithium (Eskalith, Lithobid, and others), olanzapine (Zyprexa), quetiapine (Seroquel), ziprasidone (Geodon).

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