Editorial Office,

British Journal of pharmacology **02, 24, 2021**

Dear Editor,

We would like to submit our manuscript, **"Old Drug New Use: Safety and efficacy of high-dose vitamin B6 for treating antipsychotic-induced hyperprolactinemia in male patients with treatment-resistant schizophrenia",** by Chuanjun Zhuo for consideration for publication in British Journal of pharmacology.

By this RCT study, although with limitations, we found that an old drug vB6 was more effective for reducing prolactin levels and was associated with lesser ASEs in treatment resistant schizophrenia(TRS)patients with Antipsychotic-induced hyperprolactinemia over 16 weeks. Additionally, vB6 may have cognitive benefits in this patient population. We conclude that vB6 is a promising candidate Antipsychotic-induced hyperprolactinemia treatment, a though longer-term monitoring of effects on microelement and growth hormone levels are needed.

Except vitmin B6, some other old drug new use was also reported by many studies, our study provide new evidence for re-assess the value some old drug.

This paper has not been published elsewhere in whole or in part. All authors have read and approved the content, and agree to submit it for consideration for publication in your journal. There are no ethical/legal conflicts involved in the article.

Your consideration for this manuscript is highly appreciated.

Yours sincerely,

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Article Type: Research Article

Old Drug New Use: Safety and efficacy of high-dose vitamin B6 for treating antipsychotic-induced hyperprolactinemia in male patients with treatment-resistant schizophrenia

Running Title: Vitamin B6 and hyper-prolactin

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Word count: 3040

Data availability statement

The datasets generated and analysed during the present study are available from the corresponding author on reasonable request.

Funding statement

This study was supported by the National Natural Science Foundation of China (81871052 to CJZ, 81801679 and 81571319 to YX), the Key Projects of the Natural Science Foundation of Tianjin, China (17JCZDJC35700 to CJZ), the Tianjin Health Bureau Foundation (2014KR02 to CJZ), the Talent Fund of Tianjin Anding 300,000 (Yuan RMB) to CJZ.

Author contribution statement

Chuanjun Zhuo had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis. Haibo Wang and Yong Xu contributed equally as co-first authors.

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Conflict of interest disclosures

All authors completed and submitted the ICMJE Form for Disclosure of Potential Conflicts of Interest and none were reported.

Role of the funder/sponsor

The funder had no role in the design and conduct of the study; collection, management, analysis, and interpretation of the data; preparation, review, and approval of the manuscript; or the decision to submit the manuscript for publication.

Acknowledgements

We thank Professor Andrea Cipriani from Department of Psychiatry, University of Oxford, Oxford, UK (He taught me how to design a good study and analyze the results. In my heart, he is my mentor) and Professor Weihua Yue from Peking university for providing constructive suggestions for the study.

Ethics approval statement

The protocol for this study, which is a double-blinded randomized control trial, was approved by our hospital's institutional review board (TK-IRB-2017-C-01). All procedures performed in studies involving human participants were in accordance with the ethics standards of the institutional and national research committee and with the 1964 Helsinki Declaration and its later amendments or comparable ethics standards.

Trial Registration: ChiCTR1800014755

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Not applicable

Abstract

Background and Purpose: This study aimed to investigate the safety and efficacy of high-dose vitamin B6 (vB6) for antipsychotic-induced hyperprolactinemia (AIHP)

treatment in male patients with treatment-resistant schizophrenia (TRS).

Experimental Approach: In this randomized double-blinded controlled study, patients were randomized (1:1) into a control group given aripiprazole (ARI; 10 mg/day) or an intervention group given vB6 (300 mg/12 h for 16 weeks). Prolactin level, psychotic symptoms [Positive and Negative Syndrome Scale (PANSS)], cognitive function [MATRICS Consensus Cognitive Battery (MCCB)], liver function, kidney function, growth hormone level, micronutrient levels, blood lipids, and adverse secondary effects (ASEs)[Treatment Emergent Symptom Scale (TESS) and Barnes-Akathisia scale] were monitored.

Key Results: After a 16-week treatment period, the vB6 group showed a 68.1% reduction in serum prolactin levels (from 95.52 ± 6.30 μg/L to 30.43 ± 18.65 μg/L) while the ARI group showed only a 37.4% reduction (from 89.07 ± 3.59 μg/L to 55.78 ± 7.39 μg/L). During weeks 1–4, both treatments reduced prolactin similarly. Subsequently, the ARI effect plateaued, while the vB6 effect remained robust. AIHP reduction efficacy of vB6 was associated with baseline prolactin and triglyceride levels, total vB6 dosage, and education level.

Conclusion and Implications: Compared with the ARI group, TRS patients given vB6 showed better attenuation of AIHP, lower ASE scores, and improvements in clinical symptoms and cognitive impairments. These results support further consideration of vB6 as a putative treatment for AIHP.

Key words: TRS, Aripiprazole, Drug repurposing, Cognitive ability, PANSS

Bullet point summary

What is already known

Antipsychotic-induced hyperprolactinemia (AIHP) is a difficult to manage secondary adverse effect (ASE) of antipsychotic medication use. Recommendations for reducing the risk of or alleviating AIHP, beyond low-dosage ARI, including metformin, traditional Chinese herbs, and low-dosage dopamine agonists (e.g. bromocriptine). However, these approaches are not highly satisfactory, especially with respect to the management of psychotic symptoms.

What this study adds

vB6 was more effective for reducing prolactin levels and was associated with lesser ASEs in treatment resistant schizophrenia(TRS)patients with AIHP over 16 weeks. Additionally, vB6 may have cognitive benefits in this patient population. We conclude that vB6 is a promising candidate AIHP treatment, though longer-term monitoring of effects on microelement and growth hormone levels are needed.

Clinical significance

vB6 was more effective for reducing prolactin levels and was associated with lesser ASEs in treatment resistant schizophrenia(TRS)

Introduction

Antipsychotic-induced hyperprolactinemia (AIHP) is a difficult to manage secondary adverse effect (ASE) of antipsychotic medication use . The etiology of AIHP is unclear . The main proposed mechanisms of the pathogenesis of AIHP are the estrogen protection hypothesis and the stress prolactin-dopamine hypothesis , both of which involve alterations in dopamine receptor activation . Each of these hypotheses provides only a partial explanation. Accordingly, the need for more studies examining functional disturbances of the hypothalamic-pituitary-gonadal axis in patients with psychosis has been emphasized . The clinical manifestations of hyperprolactinemia, including sexual dysfunction and gynecomastia in male patients, can cause patients to feel distressed and to suffer a reduction of life quality and thus result in reduced compliance with antipsychotic treatment adherence and, ultimately, a deteriorated prognosis .

Several decades of research have not produced complete alleviation of AIHP , especially in patients with treatment-resistant schizophrenia (TRS). In most cases, patients with TRS need antipsychotic dosages two to three times the regular dosage regime and may still suffer from clinically significant residual symptoms . The long-term and high-dosage characteristics of their antipsychotic treatment increases the risk of serious ASEs, including difficult to treat hyperprolactinemia . In an effort to alleviate AIHP, many physicians will switch patients from high-dosage antipsychotics to low-dosage aripiprazole (ARI) , which has been suggested to alleviate the condition in at least some cases , albeit not without some controversy . Recommendations for reducing the risk of or alleviating AIHP, beyond low-dosage ARI, including metformin,

traditional Chinese herbs, and low-dosage dopamine agonists (e.g. bromocriptine) . However, these approaches are not highly satisfactory, especially with respect to the management of psychotic symptoms.

Some older studies examining the effects of the water-soluble micronutrient vitamin B6 (vB6), may be relevant to the problem of AIHP. In 1977, Delitala et al. found 600-mg vB6 injections reduced prolactin levels in patients using antipsychotics and reported a pharmacodynamic curve of the resultant altered prolactin levels over several hours . In a 1978 study of lactating women, de Waal et al. found that vB6 (300–1200 mg) did not reduce chlorpromazine-induced hyperprolactinemia, but perhaps this negative conclusion should be re-considered given that the women were actively producing milk, a physiological process that requires elevated prolactin . Indeed, in 1979, Rosenberg et al. reported that vB6 reduced chlorpromazine-induced hyperprolactinemia in animal models . Following these studies, however, the safety and potential efficacy of vB6 for reducing elevated prolactin levels in patients taking antipsychotics were not established.

Patients have been given vB6 to alleviate nausea and vomiting (due to pregnancy or radiation sickness) and to alleviate premenstrual/menstrual breast pain; it has been suggested that it works for these conditions by promoting dopamine production in the brain, thus activating dopamine receptors that reduce the secretion of pituitary prolactin . Furthermore, vB6 has been shown to suppress postpartum lactation at a dosage of 600 mg/day and to reduce homocysteine serum levels at a dosage of 1200 mg/day without any obvious ASEs after 12 weeks of use .

Recent methodological advancements have enabled researchers to discover previously unrecognized effects of old drugs. For example, antipsychotic agents have been shown to have surprising anticancer effects ; and metformin has been reported to delay cognitive decline in patients with Alzheimer's disease and to alleviate chronic pain . Additionally, vB6 supplementation has been shown to have immune function benefits in vB6-deficient people , and vB6 is a potent antioxidant that quenches reactive oxygen species and thus supports cellular health . Although the mechanism by which vB6 reduces prolactin levels has not been delineated, vB6 therapy appears to have a favorable benefit-risk ratio given that ASEs of vB6, especially neurological ASEs, are rare . Based on the aforementioned findings, we were inspired to re-assess the potential efficacy of vB6 for the alleviation of AIHP.

The aim of the present study was to test the effects of high-dosage vB6 on AIHP, compared to the effects of ARI, in patients with TRS. We hypothesized that high-dosage vB6 would (1) reduce prolactin levels at least as well as ARI, (2) result in a lower ASE load than ARI, and potentially (3) help to alleviate cognitive impairments in patients with TRS.

Methods

Participants and study design

A total of 200 patients with TRS were recruited from Tianjin Kangtai Hospital (a mental health treatment center) from August 1st, 2018 to July 31st, 2020. The protocol for this study, which is a double-blinded randomized control trial, was approved by our

hospital's institutional review board (TK-IRB-2017-C-01). All participants and their guardians signed written informed consent forms after receiving a complete explanation of the study. To avoid menstrual cycle effects on prolactin , we recruited only male patients. The participants were divided (1:1) into two groups according to a random number table. One group received vB6 and the other received ARI for 16 weeks.

The inclusion criteria were as follows: (1) male; (2) diagnosis of TRS according to the criteria recommended by Kane ; (3) age, 20~45 years; (4) consistent antipsychotic dosage for at least 1 month prior and during the 16-week study duration; and (5) willingness to participate and sign the informed consent form. Regarding criterion 4, it should be noted that patients were permitted to receive sedatives for the treatment of psychotic symptoms or acute agitation. The exclusion criteria were as follows: (1) allergy to vB6 or ARI; (2) diagnosis of intellectual disability, substance abuse disorder, or other psychiatric disorder besides schizophrenia; (3) history of epilepsy, head trauma, neurological disease, or systemic disease (e.g. internal organ, blood, endocrine, and metabolic diseases; mild blood glucose deviations were not considered exclusionary); 4) history of suicide attempts or serious suicidal ideation; and (6) inability to follow the study protocol.

Treatments

Patients were given oral vB6 at a dosage of 300 mg/12 h (600 mg/day total) as an experimental therapy or oral ARI at the recommended dosage of 5 mg/12 h (10 mg/day total), which has been shown to reduce AIHP . Pills were taken at approximately 8:00

a.m. and 8:00 p.m. On the days that blood samples were collected, the morning pill was taken immediately after the blood draw.

Treatment monitoring and efficacy measures

All patients were monitored with the following assessments every 4 weeks. Psychotic symptoms and cognitive functioning were monitored with the Positive and Negative Syndrome Scale (PANSS) and MATRICS Consensus Cognitive Battery (MCCB), respectively. Blood samples were collected for liver and kidney functional enzyme, microelement (iron, calcium, copper, potassium, and sodium), and human growth hormone measurements. ASEs were monitored with the Treatment Emergent Symptom Scale (TESS) and Barnes-Akathisia scale. Serum vB6 and ARI concentrations were determined by high-performance liquid chromatography–tandem mass spectrometry. The inter-assay precision for all analyses was <10% .

Statistical analysis

The data were analyzed in SAS statistical software (version 9.3, SAS Institute, Cary, NC). The data are expressed in the form of mean ± standard deviation (normally distributed data) or median ± interquartile range (non-parametric continuous-variable data) or numbers and percentages (categorical variables). Differences between the two groups were detected with Student's t tests, Wilcoxon rank sum tests, and chi-square/Fisher's exact tests, as appropriate. The efficacy analysis followed the intention-to-treat principle. To correct for missing values the last observation carried

forward method was used. Repeated-measures general linear models were employed to evaluate the effects of time and treatment on prolactin levels after adjusting for age, education level, total drug dose, triglyceride levels, and cholesterol levels. Improvement rate was defined as the proportion of participants achieving a serum prolactin level <40 ng/ml. Among the participants treated with vB6, univariate and multivariate associations of clinical-demographic characteristics with an improvement of serum prolactin level were evaluated with a logistic regression model and expressed as odds ratios (ORs) with 95% confidence interval (CIs).

Results

Demographic and clinical characteristics

As described in the study enrollment and retention flow chart shown in Figure 1, of 260 patients with TRS who were recruited, 200 were eligible for inclusion in the study and assigned randomly to the ARI group (N = 100) or vB6 group (N = 100). A total of 6 patients in the ARI group dropped out (dropout rate, 1.5%), including 3 patients due to worsening of psychotic symptoms (they were given increased clozapine dosage and electroconvulsive therapy), 2 patients due to bacterial infection (they were given anti-inflammation treatment), and 1 patient who did not want to continue the study but did not provide a reason. No patients dropped out of the vB6 group. The full 200 patients were included in the intention-to-treat analyses. The two groups were similar with respect to clinical characteristics (Table 1).

Treatment efficacy

From baseline levels to the end of the 16-week study period, the vB6 group showed a 68.1% reduction in prolactin levels from 95.52 ± 6.30 μg/L to 30.43 ± 18.65 μg/L while the ARI group showed a 37.4% reduction from 89.07 ± 3.59 μg/L to 55.78 ± 7.39 μg/L. From baseline to week 4, both groups demonstrate similarly steep reductions in prolactin levels. However, the trends diverged subsequently, especially after week 8 when the efficacy of ARI plateaued. Meanwhile, vB6 continued to further reduce prolactin levels through week 16. Repeated-measures general linear models showed a significant group × time interaction effect on prolactin levels ($F = 99.03$, $p < .001$). The statistical results of inter-group comparisons are reported in Table 2 and Figure 2.

Factors associated with prolactin reduction

Multivariate logistic regression model analysis revealed four factors as being significantly related to prolactin level reduction to <40 μg/L at week 16: education level; total drug dose at the conclusion of week 16; baseline triglyceride level; and baseline prolactin level. The resultant ORs, CIs, and *p* values are reported in Table 3 and Supplemental Table 1.

Psychometric measures

Psychometric scores obtained for the two groups are shown in Table 4. The vB6 group had significantly better (lower) PANSS scores than the ARI group at baseline, week 4, and week 16. The vB6 group exhibited a 17.8% reduction in PANSS scores from baseline to week 16, while the ARI group exhibited only an 11.96% reduction (*p*

< .001). MCCB total scores were similar between the two groups at baseline, but higher in the vB6 group than in the ARI group by week 16.

With respect to cognitive performance, the vB6 group showed an average increase in MCCB total score of 9.94% during the study period, while the ARI group showed a decrease of 5.43% (p < .001). The only MCCB subscore that differed significantly between the groups was the working memory score. None of the patients in the vB6 group experienced a clinically significant deterioration in psychotic symptoms (PANSS score increase of ≥15%). Meanwhile, 4 patients in the vB6 group experienced a clinically significant improvement in psychotic symptoms (≥50% reduction in PANSS score). In the patients in the ARI group, 4 patients experienced a clinically significant deterioration in psychotic symptoms (including 3 who dropped out) and 2 patients showed a clinically significant improvement.

Safety and tolerance

According to Barnes-Akathisia scale and TESS scores (Table 4), the vB6 group experienced lesser ASEs than the ARI group. The most frequently observed ASEs overall were drowsiness (73.5%, 147/200), akathisia (64.5%, 129/200), dizziness (56.5%, 113/200), constipation (58.50%, 117/200), hand tremor (50.5%, 101/200), salivation (47.0%, 94/200), transient arrhythmia (31.5%, 53/200), and orthostatic hypotension (23.5%, 47/200). The incidences of these ASEs did not differ significantly between the two groups (data not shown). Thus, the aforementioned significant

differences in scale scores can thus be attributed in large part to the greater severity of ASEs in the ARI group, consistent with our general clinical observations. More importantly, the blood sugar, liver and kidney function had none significant difference between two groups (Supplemental Table 2). However, triglycerides and cholesterol had significant difference between groups, vB6 group, the level of triglycerides and cholesterol was lower (Supplemental Table 2).

Discussion

In the present study, our results demonstrate, for the first time to our knowledge, that high-dosage vB6 reduces elevated prolactin in patients with TRS as effectively as ARI in the first 4 weeks of treatment and more effectively than ARI thereafter. Our data also suggest that vB6 had a beneficial effect on cognition. Our data also suggest that vB6 had a beneficial effect on cognition. No serious ASEs were observed in this study in either group. Overall, we observed an encouraging safety and efficacy profile for vB6 in TRS patients needing AIHP treatment.

The mechanism underlying improved PANSS scores in the vB6 group are unknown. It is possible that these benefits are related to the neuroprotective and anti-inflammatory effects of vB6. Concurrent improvements in PANSS scores in the ARI group could reflect an augmentation effect of ARI relative to the previous antipsychotic agent that the patient had been using. Similar ASEs emerged in the two groups, including drowsiness, constipation, dry mouth, akathisia, hydro-stomia, transient arrhythmia, and orthostatic hypotension. Thus, treating physicians should be vigilant in

looking for signs of ASEs. Notably, it is important to treat constipation, which can lead to hyperammonemia .

According to the estrogen protection hypothesis of AIHP, increases in estrogen levels, which can modulate psychotic symptoms in schizophrenia , lead to competitive antagonism of inhibitory type 2 dopamine (D2) receptors in the pituitary. Normally, dopamine binding to D2 receptors inhibits prolactin secretion from prolactin secreting cells. Thus, antagonism of D2 receptors results in increased secretion of prolactin . The stress-prolactin-dopamine hypothesis is informed by observations indicating that prolactin itself can act as a stress hormone, being released in response to stressful stimulation. This stress-induced prolactin release may then trigger a positive feedback mechanism in which increased dopamine release triggers further prolactin elevation, while also potentially worsening psychotic symptoms . Elevations in prolactin may then suppress gonadal estrogen production as a negative feedback adaption. Interestingly, schizophrenic patients with hyperprolactinemia have been reported to have increased pituitary volumes, consistent with the stress-prolactin-dopamine hypothesis . These two hypotheses converge in suggesting that D2 receptor activation in prolactin cells in the pituitary plays a pivotal role in AIHP.

Supplemental vB6 can enhance hypothalamic/pituitary dopaminergic neuron activity, increase dopamine levels, and thus reduce competitive antipsychotic drug occupation of D2 receptors while enabling dopamine to inhibit secretion from prolactin cells . In another study, vB6 was reported to inhibit prolactin secretion partially via a dopamine-independent mechanism . ARI is a partial D2 receptor agonist with effects

that are often sufficient to maintain prolactin within physiological levels . Hence, based on the available evidence, it appears that vB6 influences prolactin levels via a mechanism or mechanisms different from that of ARI, such as enabling dopamine to inhibit prolactin hypersecretion and perhaps additionally via a dopamine-independent mechanism.

Limitations

There are a number of notable limitations in the present study. First, the average baseline prolactin level was higher and the average age was younger in the vB6 group than in the ARI group. Because patients were assigned to groups randomly and this was a double-blinded study, we could not match subjects for prolactin levels or age across the two groups. Thus, future research with a different study design should address these factors. Second, we only monitored whether microelements were within a normal range or not. More detailed blood concentration analyses were beyond the scope of our protocol. However, because blood microelement concentrations may influence efficacy or ASE risk, more detailed micronutrient analyses should be performed in this patient population. Third, because our focus was on AIHP in patients with TRS, rather than in schizophrenic patients whose psychotic symptoms are well-controlled, some patients dropped out due to symptom worsening. Fourth, because the patients had TRS, they were taking relatively high doses of antipsychotics compared to the average schizophrenic patient and thus had quite high prolactin levels, relative to other studies in the literature. The efficacy of vB6 in treatment-responsive schizophrenic patients

remains to be determined. Fifth, although we did not find that microelement or growth hormone levels were significantly altered in the vB6 group, we only monitored patients for 16 weeks. Longer-term monitoring data are thus needed. Sixth, we did not divide the patients into subgroups according to the particular antipsychotic agent they were using.

Conclusion

Compared to ARI, vB6 was more effective for reducing prolactin levels and was associated with lesser ASEs in TRS patients with AIHP over 16 weeks. Additionally, vB6 may have cognitive benefits in this patient population. We conclude that vB6 is a promising candidate AIHP treatment, though longer-term monitoring of effects on microelement and growth hormone levels are needed.

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Figure legends

Figure 1. Flow chart of patient enrollment and retention in the study.

Figure 2. Least-squares mean change in serum prolactin levels from baseline to week 16 in men with TRS. The data were adjusted for age, education level, total drug dosage, blood triglyceride level, and blood cholesterol level. Note that although the vB6 group had, on average, higher serum prolactin levels than the ARI group, by week 4 both had achieved similarly pronounced reductions. Moreover, after week 4, prolactin levels leveled off in the ARI group while continuing to reach lower levels in the vB6 group.

Table 1. Demographic and clinical characteristics at baseline, medication use, and biochemical assessment during treatment in patients with TRS by treatment group.

Variable		ARI (N = 100)	vB6 (N = 100)	*P*
Age, years		33.65 ± 3.03	29.99 ± 4.92	**<.001**
Education	≤12 years	84 (84.0)	66 (66.0)	**.003**
	>12 years	16 (16.0)	34 (34.0)	
Disease duration before admission, weeks		6.09 ± 1.54	6.06 ± 1.41	.40
Psychiatric family history	No	74 (74.0)	79 (79.0)	.89
	Yes	26 (26.0)	21 (21.0)	
Total drug dose in 16 weeks		71,260.00 ± 9,424.43	70,262.00 ± 10,359.23	.48
PANSS at baseline		91.63 ± 6.98	89.11 ± 3.56	**.002**
Overall MCCB at baseline		29.82 ± 8.84	29.69 ± 9.17	.92
Baseline data test data				
Dose, mg/d		490.55 ± 368.63	452.02 ± 39.76	.30
Blood glucose, mmol/L		5.05 ± 0.59	5.02 ± 0.43	.71
Triglycerides, mmol/L		1.37 ± 0.29	1.57 ± 0.07	**<.001**
Cholesterol, mmol/L		4.79 ± 0.85	5.00 ± 0.16	**.02**
Alanine aminotransferase, U/L		47.80 ± 12.72	47.95 ± 12.66	.93
Aspartate aminotransferase, U/L		46.60 ± 11.97	46.04 ± 11.98	.74
Gamma-glutamyl transferase, U/L		58.20 ± 11.33	58.88 ± 11.91	.68
Creatinine, U/L		75.06 ± 16.06	74.09 ± 16.71	.68
Blood urea nitrogen, U/L		3.63 ± 0.53	3.60 ± 0.52	.77
Prolactin, μg/L		89.07 ± 3.59	95.52 ± 6.30	**<.001**

Table 2. Prolactin levels from baseline through week 16 in men with TRS.

Variable		ARI (N = 100)	vB6 (N = 100)	*P*
Serum prolactin, µg/L	Baseline	89.07 ± 3.59	95.52 ± 6.30	**<.001**
	Week 4	56.06 ± 6.73	59.72 ± 13.09	**.01**
	Week 8	53.37 ± 6.79	49.55 ± 13.00	**<.001**
	Week 12	55.45 ± 6.76	41.19 ± 15.12	**<.001**
	Week 16	55.78 ± 7.39	30.43 ± 18.65	**<.001**
Proportion with prolactin <40 µg/ml	Week 4	1 (1.0)	7 (7.0)	.06
	Week 8	2 (2.0)	22 (22.0)	**<.001**
	Week 12	1 (1.0)	48 (48.0)	**<.001**
	Week 16	2 (2.0)	67 (67.0)	**<.001**

Repeated-measures general linear models showed a significant group × time interaction effect on prolactin level ($F = 99.03$, $p < .001$).

Table 3. Factors associated with improvement of serum prolactin level to <40 μg/ml at week 16 among participants treated with vB6 as indicated by multivariate logistic regression modeling.

Factor	**OR (95% CI)**	***P***
Education level (>12 years vs. ≤12)	2.79 (1.34–5.80)	**.006**
Total drug dose in 16 weeks	0.10 (0.01–0.85)	**.04**
Triglycerides at baseline	23.47 (3.02–182.43)	**.003**
Prolactin at baseline	1.11 (1.04–1.17)	**<.001**

Table 4. Cognitive, psychotic symptom, and ASE scores at baseline and after 16 weeks in patients with TRS.

Psychometric measure		**ARI (N = 100)**	**vB6 (N = 100)**	***P***
Cognitive (sub)scale				
Brief Assessment of Cognition in	Baseline	31.81 ± 9.68	31.74 ± 9.25	.96
Schizophrenia-Symbol Coding	Week 16	31.28 ± 9.04	30.23 ± 9.29	.42
Fluency	Baseline	30.26 ± 7.54	29.16 ± 9.47	.36
	Week 16	30.26 ± 7.34	30.39 ± 8.87	.91
Trail-making test, part A	Baseline	29.68 ± 7.06	29.58 ± 9.02	.93
	Week 16	29.33 ± 8.32	31.44 ± 8.19	.07
Attention/vigilance	Baseline	29.19 ± 8.22	28.09 ± 9.03	.37
	Week 16	30.40 ± 8.23	30.61 ± 8.54	.86
Wechsler Memory Scale-III, Symbol	Baseline	29.91 ± 8.23	28.58 ± 8.60	.27
Span	Week 16	30.11 ± 8.16	31.46 ± 8.27	.25
Letter number sequencing	Baseline	31.03 ± 8.45	30.99 ± 8.61	.97
	Week 16	29.11 ± 8.58	29.98 ± 8.52	.47
Hopkins Verbal Learning Test–	Baseline	27.86 ± 8.44	30.65 ± 9.39	**.03**
Revised	Week 16	29.91 ± 8.39	29.66 ± 8.73	.84
Brief Visuospatial Memory Test–	Baseline	28.73 ± 8.43	30.58 ± 9.10	.14
Revised	Week 16	30.59 ± 8.55	30.58 ± 9.10	.99
Neuropsychological assessment	Baseline	29.86 ± 8.39	29.88 ± 8.91	.99
battery mazes	Week 16	30.39 ± 9.31	28.88 ± 8.90	.24
Mayer-Salovey-Caruso Emotional	Baseline	30.34 ± 9.22	30.53 ± 9.58	.89
Intelligence Test, Managing Emotions	Week 16	27.97 ± 9.94	29.56 ± 9.46	.25
MCCB total score	Baseline	29.82 ± 8.84	29.69 ± 9.17	.92
	Week 16	28.20 ± 8.90	32.64 ± 9.65	**<.001**
Psychotic symptoms				
PANSS	Baseline	91.63 ± 6.98	89.11 ± 3.56	**0.002**
	Week 4	85.06 ± 10.57	88.66 ± 3.71	**0.002**
	Week 8	82.4 ± 12.49	82.30 ± 8.64	0.95
	Week 12	80.2 ± 14.53	78.27 ± 11.03	0.29
	Week 16	80.67 ± 14.59	73.27 ± 17.19	**0.001**
ASEs				
Barnes-Akathisia	Baseline	2.83 ± 4.15	1.93 ± 3.96	.12
	Week 4	4.02 ± 5.10	2.51 ± 4.40	**.03**
	Week 8	4.42 ± 5.71	2.44 ± 4.77	**.008**
	Week 12	4.66 ± 5.96	2.47 ± 4.76	**.005**
	Week 16	4.45 ± 5.84	2.32 ± 4.65	**.005**
TESS	Baseline	1.88 ± 0.54	1.77 ± 0.47	.12
	Week 4	1.89 ± 0.55	1.75 ± 0.50	.06
	Week 8	1.89 ± 0.55	1.64 ± 0.54	**.001**

Week 12	1.88 ± 0.54	1.60 ± 0.53	**<.001**
Week 16	1.89 ± 0.55	1.63 ± 0.56	**.001**