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L-Theanine Relieves Positive, Activation, and Anxiety Symptoms in Patients With Schizophrenia and Schizoaffective Disorder: An 8-Week, Randomized, Double-Blind, Placebo-Controlled, 2-Center Study

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Objective: L-Theanine is a unique amino acid present almost exclusively in the tea plant. It possesses neuroprotective, mood-enhancing, and relaxation properties. This is a first study designed to evaluate the efficacy and tolerability of L-theanine augmentation of antipsychotic treatment of patients with chronic schizophrenia and schizoaffective disorder.

Method: 60 patients with *DSM-IV* schizophrenia or schizoaffective disorder participated in an 8-week, double-blind, randomized, placebo-controlled study. 400 mg/d of L-theanine was added to ongoing antipsychotic treatment from February 2006 until October 2008. The outcome measures were the Positive and Negative Syndrome Scale (PANSS), the Hamilton Anxiety Rating Scale (HARS), the Cambridge Neuropsychological Test Automated Battery (CANTAB) for neurocognitive functioning, and additional measures of general functioning, side effects, and quality of life.

Results: 40 patients completed the study protocol. Compared with placebo, L-theanine augmentation was associated with reduction of anxiety (*P*=.015; measured by the HARS scale) and positive (*P*=.009) and general psychopathology (*P*<.001) scores (measured by the PANSS 3-dimensional model). According to the 5-dimension model of psychopathology, L-theanine produced significant reductions on PANSS positive (*P*=.004) and activation factor (*P*=.006) scores compared to placebo. The effect sizes (Cohen *d*) for these differences ranged from modest to moderate (0.09–0.39). PANSS negative and CANTAB task scores, general functioning, side effect, and quality of life measures were not affected by L-theanine augmentation. L-Theanine was found to be a safe and well-tolerated medication.

Conclusions: L-Theanine augmentation of antipsychotic therapy can ameliorate positive, activation, and anxiety symptoms in schizophrenia and schizoaffective disorder patients. Further long-term studies of L-theanine are needed to substantiate the clinically significant benefits of L-theanine augmentation.

**Trial Registration:** clinicaltrials.gov Identifier: NCT00372151

J Clin Psychiatry

Schizophrenia is a disabling psychiatric disorder that is characterized by positive, negative, mood, and cognitive symptoms. The majority of patients with schizophrenia exhibit functional and quality of life deficits. Using antipsychotic agents, other medicines, and nonpharmacological interventions for treating schizophrenia patients remains insufficient and incomplete. At present, debates as to whether second-generation antipsychotic drugs (SGAs) are better than first-generation antipsychotic drugs (FGAs) in the treatment of patients with schizophrenia are still ongoing.[1,2]

Neuroprotection is a property of some agents that should reverse some injuries or prevent further damage. Since there is no specific palliative medication for mental disturbances, neuroprotection has become the focus of intense research over the past few years, especially in psychiatric disorders, such as schizophrenia,[3,4] associated with progressive brain tissue loss. Therefore, it is opportune to look for compounds in order to achieve brain protection. This subject is one of the current challenges for both psychiatrists and neuroscientists.

The majority of neuroprotective agents are biologically active natural products, either plant extracts or endogenous peptides/proteins. Gamma-ethylamino-L-glutamic acid (L-theanine) is a biologically active natural product that is present almost exclusively in the tea plant, *Camellia sinensis*, where it is typically found in concentrations from 1% to 2% of dry weight.[5] L-Theanine can pass the blood-brain barrier, and it has various neurochemical effects on the brain.[6–8]

The main effect of L-theanine is neuroprotective. In particular, L-theanine directly provides neuroprotection against focal cerebral ischemia,[9–11] and it appears capable of preventing cell death caused by kainic acid.[12] It also protects against glutamate neurotoxicity and stimulates the release of nerve growth factor.[13] Animal studies indicate possible neuroprotective effects of L-theanine in the hippocampus through blockade of multiple glutamate receptor subtypes, *N*-methyl-D-aspartate (NMDA), and α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA) receptors.[11,12,14] L-Theanine directly provides neuroprotection against

Figure 1. Flow Diagram of the Study Population
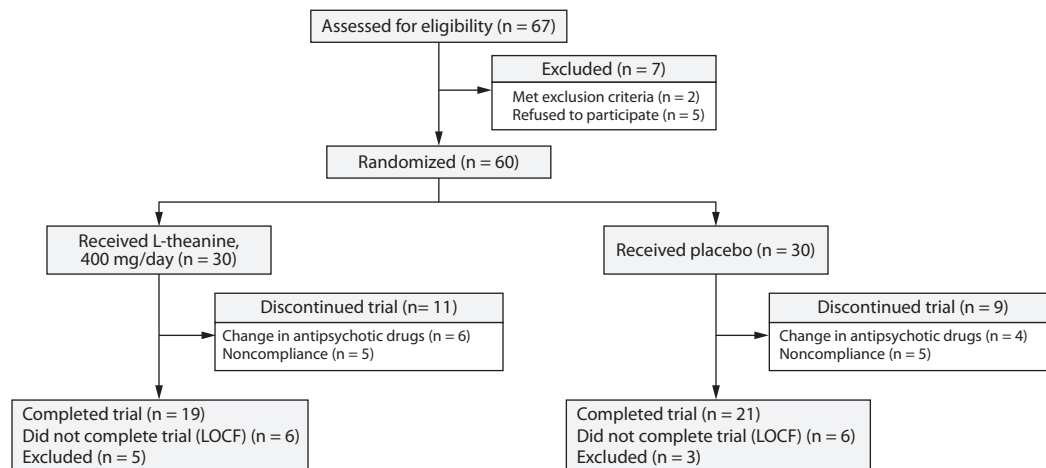
Parkinson's disease–related neurotoxic agents, while pretreatment with L-theanine significantly attenuates the down-regulation of brain-derived neurotrophic factor and glial cell line-derived neurotrophic factor production in cultured human dopaminergic cell lines.[13] The neuroprotective effect of theanine is mediated, at least in part, by γ-aminobutyric acid (GABA_A) receptors.[15] Kakuda and colleagues[12] suggest that the mechanism of the neuroprotective effect of L-theanine is related not only to the glutamate receptor but also to other mechanisms such as the glutamate transporter.

Other effects of L-theanine are mood-enhancing[12,16,17] and relaxation,[18] which may be explained by the effects of L-theanine on neurotransmitters in the brain, such as dopamine (DA), and serotonin (5-hydroxytryptamine, or 5-HT)[7,19,20]; L-theanine may inhibit excitatory neurotransmission and cause inhibitory neurotransmission via glycine receptors.[8,21] Some neurochemistry studies report that L-theanine increases brain DA, 5-HT, and GABA levels, and it has micromolar affinities for AMPA, kainate, and NMDA receptors.[7,22] L-Theanine was also reported to induce reduction of glutamate reuptake by inhibition of glutamate transporter.[23]

The antioxidant activity of L-theanine has been studied in regard to its effect on the oxidation of low-density lipoprotein (LDL) cholesterol. In vitro testing, using malondialdehyde as a marker of lipid peroxidation, demonstrated inhibition of LDL oxidation with L-theanine, although the effect was weaker than with the potent antioxidant effect of green tea polyphenols.[24] Thus, L-theanine displays a neuropharmacology suggestive of a possible neuroprotective, psychological stress–reducing, and cognitive enhancing agent, and it warrants further investigation in animals and humans. Although there are many investigations into the neuroprotective ability of L-theanine, it is not approved for any therapeutic use in the United States and other Western countries.

To date there is no study that demonstrates the neuroprotective activity of L-theanine in amelioration of any neurodegenerative condition. To the best of our knowledge, no clinical trials with L-theanine in patients with schizophrenia and schizoaffective disorder have been published. In this article, we report data from a clinical double-blind study that examined the efficacy and tolerability of L-theanine as add-on therapy to antipsychotic treatment. Given the neuroprotective and neuromodulatory potential roles of L-theanine, we hypothesized that L-theanine augmentation of ongoing antipsychotic therapy would improve both psychotic symptoms and cognitive performance in chronic schizophrenia and schizoaffective disorder patients, and to a greater extent than placebo administration.

METHOD

Patients

From February 2006 to October 2008, 67 patients with schizophrenia or schizoaffective disorder were consecutively recruited among the inpatient and outpatient services of 2 large state referral hospitals: the Sha'ar Menashe Mental Health Center and the Be'er-Sheva Mental Health Center, Hadera, Israel. Of all screened subjects, 7 patients did not enter the study; 2 subjects were excluded due to comorbidity with substance abuse, and 5 patients declined to participate (Figure 1). Sixty patients were randomized to receive L-theanine or placebo (30 patients in each group). The study sample consisted of 12 women and 48 men. The mean (SD) age of the subjects was 36.4 (11.5) years (range, 19–55 years), and mean education was 11.4 (SD = 2.4) years (range, 6–18 years). Five percent (n = 3) were married, 76.7% (n = 46) were single, and 18.3% (n = 11) were divorced or widowed. Mean age at onset of illness was 24.4 (SD = 9.1) years (range, 9–43 years), mean duration of illness was 12.3 (SD = 8.6) years (range, 2–30 years), and mean number of admissions was 8.6 (SD = 9.3) (range, 1–30). Forty-eight subjects met *Diagnostic and Statistical Manual of Mental Disorders*, Fourth Edition (*DSM-IV*) criteria for paranoid schizophrenia, while 12 met *DSM-IV* criteria for schizoaffective disorder.

At baseline, the L-theanine and placebo groups were matched by means of sex ($\chi^2_1 = 3.7$, $P = .062$), marital status ($\chi^2_2 = 0.5$, $P = .77$), distribution of diagnoses (schizophrenia or schizoaffective disorder, $\chi^2_1 = 0.4$, $P = .52$), patients' age, age at illness onset, number of hospitalizations, duration of disease, and body mass index (all P values > .05). Twenty-one patients were treated with the FGAs chlorpromazine, haloperidol, haloperidol decanoate, perphenazine, zuclopenthixol, zuclopenthixol decanoate, and fluphenazine decanoate; 25 patients were treated with the SGAs clozapine, risperidone, olanzapine, quetiapine, ziprasidone, and amisulpride; and 14 patients received both types of antipsychotic medications (combined therapy). Allocation in this study was independent of FGA, SGA, or combined therapy treatment group ($\chi^2_2 = 1.7$, $P = .42$). Mean (SD) chlorpromazine equivalents in the FGA group were 564 (315) mg/d, in the SGA group were 450 (227) mg/d, and in the combined therapy group were 638 (368) mg/d (analysis of variance [ANOVA], $F_{2,60} = 1.3$, $P = .27$).[25,26] Besides the antipsychotic medications, the patients continued taking the anticholinergics and benzodiazepines that they received prior to the study recruitment. The enrolled patients were not treated with antidepressants.

Study Design

This was an 8-week, 2-center, fixed-dose trial with 400 mg/d L-theanine as add-on to on-going antipsychotic treatment.

Inclusion criteria were (1) duration of illness longer than 2 years, (2) age from 18 to 60 years, (3) at least 2 weeks of ongoing constant antipsychotic treatment before the study entry, and (4) ability and willingness to sign informed consent. Major exclusion criteria included (1) an unstable mental condition, (2) any significant physical or neurologic illness, (3) pregnancy, and (4) treatment with mood stabilizers. The absence of medical or neurologic illnesses was verified by means of a routine laboratory investigation, physical and neurologic examinations, reports of the patient's family physician, and medical records. It was forbidden to add any other psychoactive medication before entry or during the entire study period. Prior to starting the study, all subjects provided written informed consent after receiving a full explanation regarding the nature of the study and its potential risks and benefits. The study was approved by the institutional review boards of the 2 participating centers and the national Ministry of Health Ethical Review Board. The study was registered at clinicaltrials.gov (NCT00372151).

Senior psychiatrists (M.S.R., C.M., Y.R., T.S., and V.L.) at each site enrolled and established patients' diagnoses according to *DSM-IV* criteria. At the screening visit, the investigators collected background and demographic data, a family and personal history, details about the present illness, medications, and a psychiatric and general medical history. A physical examination and blood samples for laboratory analysis were done as well.

After screening and baseline assessments, patients were randomized (by means of random number generation) to receive either 400 mg/d (200 mg × 2 times/d) of L-theanine or placebo in identical capsules (Biosynergy, Boise, Idaho) for 8 weeks in a double-blind mode. The randomization procedure was performed using the Random Allocation Software (Version 1.0, May 2004; M Saghaei, MD; Department of Anesthesia, Isfahan University of Medical Sciences, Isfahan, Iran; available at: http://mahmoodsaghaei.tripod.com/Softwares/randalloc.html).

The pharmacist, who conducted randomization of participants by using a random and equal block size for placebo and L-theanine, was responsible for keeping the blinding of the trial. None of the investigators had any control over the randomization of the patients. Allocated patients' details were coded and kept confidential in the pharmacy safe until the trial was completed. Neither clinicians nor patients were able to identify the impending treatment allocation. None of the codes were broken during the trial period.

The outcome measures were collected over 5 visits: a baseline visit before starting therapy and then after 2, 4, 6, and 8 weeks. Neurocognitive tests were performed at baseline and after 4 and 8 weeks. All observed or self-reported adverse events that appeared during the study or exacerbations of preexisting illnesses were recorded. Adverse events were evaluated for severity, duration, and possible connection to the studied drug.

Outcome Measures

All outcome measures were performed by psychiatrists who were blind to the patients' medication. The primary rating tools were the Clinical Global Impressions-Severity of Illness scale (CGI-S),[27] the Positive and Negative Syndrome Scale (PANSS),[28] the Calgary Depression Scale for Schizophrenia (CDSS),[29] and the Hamilton Anxiety Rating Scale (HARS).[27] Secondary outcome measures included the computerized Cambridge Automated Neuropsychological Test Battery (CANTAB),[30,31] the Global Assessment of Functioning (GAF),[32] the Extrapyramidal Symptom Rating Scale (ESRS),[33,34] the Quality of Life Scale (QLS),[35] and the Quality of Life Enjoyment and Satisfaction Questionnaire-abbreviated version (Q-LES-Q-18).[36]

The CANTAB battery tests, which run on an IBM-compatible personal computer with a touch-sensitive screen, are grouped into the following cognitive domains: attention, memory, and executive functions. In particular, the tests included Matching to Sample Visual Search (a speed/accuracy trade-off task, testing the subject's ability to match visual samples), Delayed Matching to Sample (a test of perceptual matching, immediate and delayed visual memory, in a 4-choice simultaneous and delayed recognition memory paradigm), Pattern Recognition Memory, Rapid Visual Information Processing (sustained attention), and Stockings of Cambridge. The nonverbal nature of the CANTAB tests makes them largely language-independent and culture-free. Performance on neurocognitive tests was presented using the standard z score, which is given as the number of standard deviations ($\pm$ SD) from the mean performance computed relative to an extensive database of raw scores for healthy

Table 1. Baseline Characteristics of Patients (n = 40) With Schizophrenia and Schizoaffective Disorder Who Completed an 8-Week Clinical Trial of L-Theanine Versus Placebo

Variable	Placebo (n = 21)	L-Theanine (n = 19)	Significance[a] Test	P
Age, mean (SD), y	32.3 (10.2)	35.4 (11.1)	t = 0.9	.35
Education, mean (SD), y	11.1 (2.3)	11.7 (2.2)	t = 0.7	.47
Age at onset, mean (SD), y	23.1 (10.9)	22.1 (7.4)	t = 0.3	.75
No. of admissions, mean (SD)	8.9 (11.5)	9.2 (9.7)	z = 0.6	.53
Duration of illness, mean (SD), y	9.3 (7.3)	12.0 (9.8)	t = 1.5	.10
Body mass index, mean (SD), kg/m²	25.6 (2.6)	25.4 (6.0)	t = 0.1	.89
Daily dose, mean (SD), mg/d[b]	520 (296)	500 (191)	t = 0.3	.80
Sex, male/female, n/n	14/7	17/2	$\chi^2_1 = 2.9$	.08
Married/single, n/n[c]	2/19	1/18	$\chi^2_1 = 1.9$[d]	.17
DSM-IV diagnosis, n			$\chi^2_1 = 0.07$	.79
Schizophrenia	17	16		
Schizoaffective disorder	4	3		

[a]Continuous variables were compared using the 2-tailed *t* test or the Wilcoxon signed rank test (*z*) for assessing the difference in medians. Differences in frequency of categorical variables were examined with the χ^2 test.
[b]Chlorpromazine equivalent.
[c]Marital status: single status includes never married, separated, divorced, and widowed.
[d]Because 2 cells had an expected value less than 5, 2-tailed Fisher exact test was also applied (*P* = .49).
Abbreviation: *DSM-IV* = *Diagnostic and Statistical Manual of Mental Disorders*, Fourth Edition.

adult subjects matched by age and sex. *Z* scores were calculated by the CANTAB program on the basis of the extensive normative database included in CANTAB. A negative value of the *z* score indicates poorer than average performance.

Statistical Analysis

Each patient had data for 5 rating periods, as described above. Patients who completed the whole study (completers) were included into statistical analysis. Due to the occurrence of dropouts, the last-observation-carried-forward procedure (LOCF) was used to analyze those subjects who completed at least 4 weeks (selected a priori) but failed to complete all 8 weeks of the study (noncompleters). Last-observation-carried-forward data were of primary interest since those results are less influenced by differential dropout rates for the L-theanine versus placebo groups.

The primary focus of the efficacy analyses was around total scores for the psychiatric rating scales. Efficacy was analyzed using 3-factor and 5-factor model scores of schizophrenia symptoms based on 30 items of the PANSS. The original 3-factor model[28] includes negative (N_1–N_7), positive (P_1–P_7), and general psychopathology (G_1–G_{16}) subscales, while the 5-factor model[37] includes positive factor (P_1, P_3, P_5, G_1, G_9), negative factor (N_1, N_2, N_3, N_4, N_6, G_5, G_7, G_8, G_{13}, G_{14}), activation factor (P_4, P_7, N_3, G_4, G_8, G_{14}), dysphoric mood factor (G_1, G2, G_3, G_4, G_6), and autistic preoccupations factor (P_3, N_5, N_7, G_{11}, G_{13}, G_{15}), which fit better to the multidimensional model describing the psychopathology of schizophrenia.[37–39]

Statistical analysis of rating scale and questionnaire scores was done with repeated-measures ANOVA using the general linear model and the Greenhouse-Geisser correction,

with 3 factors: (1) "treatment condition" (L-theanine versus placebo), (2) "time" (at baseline and at weeks 2, 4, 6, and 8), and (3) "completers versus noncompleters." In order to test the possible impact of antipsychotic treatment and *DSM-IV* diagnosis on between-group differences in outcome variables, 2 additional modifications of the ANOVA model were applied. In these models, 2 factors ("treatment condition" and "time") were entered with either drug treatment (FGAs, SGAs, combined therapy) or *DSM-IV* diagnosis (schizophrenia versus schizoaffective disorder) as the third factor. Post hoc analyses were carried out in cases of significant outcomes, using the Tukey-Kramer method and the Bonferroni correction for multiple comparisons.

Effect size (*d*) was calculated by using the method of Cohen[40] for paired samples. An effect size of 0.20 was considered small, 0.50 was considered medium, and 0.80 was considered large. Continuous variables were compared by using the 2-tailed *t* test or the Wilcoxon signed rank test (*z*) for assessing the difference in medians. Differences in frequency of categorical variables were analyzed by the χ^2 test. For all analyses, the level of statistical significance was defined as α less than .05. Statistical analyses were performed by the Number Cruncher Statistical Systems (NCSS, Kaysville, Utah).

RESULTS

Baseline Characteristics of the Experimental Groups

Forty patients (9 of 12 women and 31 of 48 men) completed the trial. The mean (SD) age of completers was 33.9 (10.6) years. Baseline demographic and clinical characteristics of these subjects are presented in Table 1.

Of 20 subjects who dropped out, 11 patients received L-theanine, while the other 9 patients received placebo. More specifically, 5 patients from the L-theanine group and 3 patients from the placebo group dropped out during the first 2 weeks of the study. Another 12 patients (6 of each treatment group) dropped out between the fourth and sixth week. Reasons for dropping out were not related to the L-theanine or placebo administration: 10 patients dropped out due to change in antipsychotic treatment (exclusion criterion) and another 10 due to noncompliance.

Eight patients, who dropped out during the first 2 weeks, were excluded from statistical analysis, while missing data of another 12 dropped-out subjects were imputed using LOCF procedure. Thus, 40 completers and 12 noncompleters were included in the data analyses (as described in the statistical analysis section).

At baseline, no significant differences in mean scores of all rating scales (PANSS, CDSS, HARS, CGI-S, GAF, ESRS, QLS, and Q-LES-Q-18) were found between the L-theanine and placebo groups (*t* test: all *P* values > .05).

Effectiveness

Psychiatric rating scales. As shown in Table 2, among the L-theanine group, a significant reduction in scores was found on PANSS positive ($F_{1,236} = 6.9$, $P = .009$) and general

Table 2. Efficacy and Safety Ratings of Patients (n = 40) With Schizophrenia and Schizoaffective Disorder Who Completed an 8-Week Clinical Trial of L-Theanine Versus Placebo[a]

Variable	Placebo (n = 21) Baseline, Mean (SD)	Placebo After 8-Week Treatment, Mean (SD)	L-Theanine (n = 19) Baseline, Mean (SD)	L-Theanine After 8-Week Treatment, Mean (SD)	First ANOVA[b] Treatment Condition $F_{1,236}$	P	First ANOVA[b] Time (5 visits) $F_{4,236}$	P	First ANOVA[b] Completers vs Noncompleters $F_{1,236}$	P	Second ANOVA[c] Type of Antipsychotic $F_{2,236}$	P	Third ANOVA[d] DSM-IV Diagnosis $F_{1,236}$	P
CGI-S	4.1 (0.7)	3.3 (0.7)	4.1 (0.6)	3.4 (0.6)	0.2	.68	9.5	<.001	1.8	.18	**12.3**	**<.001**	0.5	.48
PANSS subscale														
Positive	16.3 (5.7)	12.8 (5.4)	14.1 (3.8)	9.5 (2.2)	**6.9**	**.009**	6.4	<.001	0.1	.75	2.3	.10	3.7	.092
Negative	27.6 (7.8)	20.5 (6.4)	26.4 (8.1)	18.4 (5.6)	0.8	.36	6.0	<.001	2.0	.16	**3.6**	**.029**	0.01	.91
General psychopathology	42.2 (12.8)	32.6 (12.0)	38.0 (12.2)	26.7 (8.5)	**7.1**	**<.001**	7.0	<.001	0.5	.49	1.8	.16	1.2	.27
CDSS	4.2 (5.4)	1.0 (1.8)	2.8 (4.7)	0.7 (2.2)	0.2	.65	3.4	**.010**	1.2	.27	0.3	.77	1.0	.31
HARS	10.0 (6.1)	5.6 (5.6)	7.9 (6.0)	3.0 (3.7)	**5.9**	**.015**	4.7	<.001	1.7	.20	1.4	.24	0.3	.57
GAF	51.9 (9.1)	62.4 (11.0)	51.7 (10.0)	59.8 (9.9)	1.1	.29	6.9	<.001	3.2	.074	1.4	.24	1.7	.20
ESRS	2.8 (5.1)	2.7 (5.1)	2.3 (4.1)	1.3 (3.1)	0.1	.79	0.1	.99	2.0	.16	**8.3**	**<.001**	3.5	.087
QLS	56.2 (16.0)	58.6 (16.6)	49.3 (14.3)	53.6 (15.5)	2.6	.088	0.7	.58	3.4	.068	0.4	.65	0.1	.71
Q-LES-Q-18	3.3 (0.8)	3.6 (0.6)	3.0 (0.5)	3.5 (0.8)	0.3	.61	2.0	.088	0.1	.82	2.7	.071	0.3	.58

[a]Boldface type indicates significance at P < .05.
[b]First ANOVA model: treatment condition (L-theanine, placebo), time factor (at baseline and at weeks 2, 4, 6, and 8), and completers (completers vs discontinued patients with LOCF procedure).
[c]Second ANOVA model: treatment condition (L-theanine, placebo), time factor (at baseline and at weeks 2, 4, 6, and 8), and kind of antipsychotic drug treatment (first-generation antipsychotics, second-generation antipsychotics, combined therapy) being added to the models instead of completers with chlorpromazine equivalent (mg/d) daily dose of antipsychotics as covariate.
[d]Third ANOVA model: treatment condition (L-theanine, placebo), time factor (at baseline and at weeks 2, 4, 6, and 8), and the DSM-IV diagnosis (schizophrenia vs schizoaffective disorder) being added to the models instead of completers.
Abbreviations: ANOVA = analysis of variance; CDSS = Calgary Depression Scale for Schizophrenia; CGI-S = Clinical Global Impressions-Severity of Illness scale; DSM-IV = Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition; ESRS = Extrapyramidal Symptom Rating Scale; GAF = Global Assessment of Functioning; HARS = Hamilton Anxiety Rating Scale; LOCF = last-observation-carried-forward; PANSS = Positive and Negative Syndrome Scale; Q-LES-Q-18 = Quality of Life Enjoyment and Satisfaction Questionnaire-abbreviated version; QLS = Quality of Life Scale.

psychopathology subscales ($F_{1,236} = 7.1$, $P < .001$) in comparison to placebo.

According to the 5-factor PANSS model, in the L-theanine group, a significant decrease of scores was observed on the positive (from week 6 onward) ($F_{1,236} = 8.5$, $P = .004$), activation ($F_{1,236} = 7.8$, $P = .006$), dysphoric mood ($F_{1,236} = 5.6$, $P = .019$) (both from week 2 onward), and autistic preoccupations (from week 8 onward) ($F_{1,236} = 4.4$, $P = .037$) factors (Figure 2). However, no significant difference between the 2 groups was found on the PANSS negative subscale and negative factor scores ($P > .05$).

In addition, in the L-theanine augmentation group there was a significant amelioration of total HARS scores (onset of improvement on the second week) ($F_{1,236} = 5.9$, $P = .015$; Figure 3). Improvement was found in 5 HARS items: anxious mood ($F_{1,236} = 9.0$, $P = .003$), tension ($F_{1,236} = 5.4$, $P = .021$), intellectual (poor concentration; $F_{1,236} = 4.1$, $P = .044$), muscular (muscle aches or pains, tinnitus; $F_{1,236} = 6.4$, $P = .012$), and sensory somatic complaints ($F_{1,236} = 4.8$, $P = .030$) in comparison to the placebo group. No statistical significance was observed on the CGI-S, CDSS, GAF, and quality of life scales (Table 2, first ANOVA model).

L-Theanine augmentation was associated with modest effect sizes for the PANSS positive subscale ($d = 0.09$), activation ($d = 0.16$), and autistic preoccupations ($d = 0.15$) factor scores, whereas considerably larger effect sizes were seen for the PANSS general psychopathology subscale ($d = 0.33$), positive factor ($d = 0.29$), dysphoric mood factor ($d = 0.33$), and HARS scores ($d = 0.39$), compared with placebo.

Since 3 comparisons were significant (see Table 2, first ANOVA, treatment condition), the Bonferroni correction for 3 tests was applied ($P = .05/3 = .0166$). After the Bonferroni correction, improvement in total HARS scores and PANSS positive and general psychopathology subscales remained significant ($P < .05$). When the 5-factor model of PANSS was used instead of the 3-factor model, 5 comparisons were significant (the positive factor, activation factor, dysphoric mood factor, autistic preoccupations factor, and total HARS scores). After the Bonferroni correction ($P = .05/5 = .01$), improvement in the PANSS positive ($P = .004$) and activation ($P = .006$) factors remained significant ($P < .05$).

As Table 2 shows, both L-theanine and placebo augmentation resulted in statistically significant decreases from baseline to end point of the study on the CGI-S, PANSS, HARS, and GAF scores ("time," $df = 4,236$; all P values $< .001$) and CDSS scores ("time," $df = 4,236$; P value $< .01$), while in the ESRS, QLS, and Q-LES-Q-18 scores beneficial effect was not demonstrated (all P values $> .05$). However, no significant "treatment conditions" by "time" interactions were indicated.

Completers vs noncompleters. The trial completers did not significantly differ from the noncompleters concerning sociodemographic and clinical data or

Figure 2. PANSS Scores for an 8-Week Clinical Trial of L-Theanine (n = 30) Versus Placebo (n = 30) in Patients With Schizophrenia and Schizoaffective Disorder
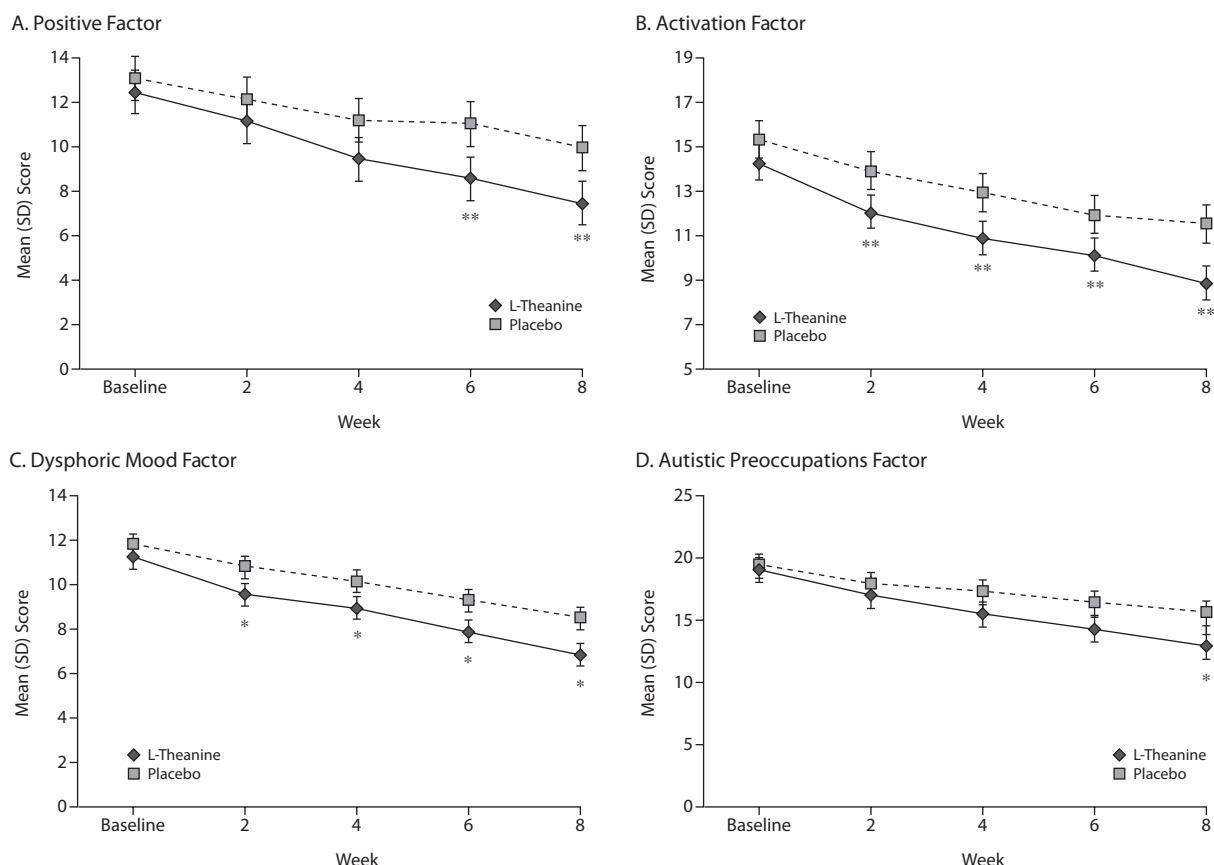
*P < .05; **P < .01.
Abbreviation: PANSS = Positive and Negative Syndrome Scale.

antipsychotic treatment (Table 1). Furthermore, there were no significant differences between the completers and non-completers on the mean scores of all rating scales for the 8-week trial period ($df = 1,236$; all P values > .05).

Neurocognitive functioning. At baseline, both groups were equal in performance of CANTAB tasks. L-Theanine and placebo did not influence this performance throughout the trial (all P values > .05).

Antipsychotic agents and DSM-IV diagnosis. Of 40 completers, 11 patients were treated with FGAs, 18 patients were treated with SGAs, and 11 patients received combined therapy. There was no difference between either group regarding the distribution of medication type ($\chi^2_2 = 0.3$, $P = .86$) and chlorpromazine equivalents (mean [SD] = 600 [332] mg/d for FGAs, 452 [222] mg/d for SGAs, and 519 [178] mg/d for combined therapy) (ANOVA, $F_{2,40} = 1.2$, $P = .30$). Moreover, there was no statistical significance between these factor × time interactions on the evaluated scores of the PANSS and HARS (all P values > .05). As expected, CGI-S, PANSS negative subscale, and ESRS scores were lower in patients of both study groups treated with SGAs compared to those treated with FGAs and combined therapy (second ANOVA model; Bonferroni multiple comparison test, all P values < .05, Table 2).

When *DSM-IV* diagnosis was entered into the ANOVA model, no significant differences in rating scales were found between schizophrenia and schizoaffective disorder patients (all P values > .05; third ANOVA model, Table 2), while the above-mentioned differences from baseline to end point for both the L-theanine and placebo groups on the PANSS and HARS scores remained statistically significant (all P values < .001).

Tolerability and Safety

No treatment-related adverse events occurred in either group. There were no clinically significant changes in vital signs, electrocardiograms, or clinical laboratory variables associated with treatment.

DISCUSSION

To the best of our knowledge, this is the first trial designed to evaluate the efficacy and tolerability of L-theanine augmentation of antipsychotic treatment in patients with chronic schizophrenia or schizoaffective disorder. The results of this study can be divided into 3 branches of findings.

The first branch, L-theanine (400 mg/d) augmentation, is associated with reduction of anxiety (assessed by HARS

Figure 3. Hamilton Anxiety Rating Scale Scores for an 8-Week Clinical Trial of L-Theanine (n = 30) and Placebo (n = 30) in Patients With Schizophrenia and Schizoaffective Disorder
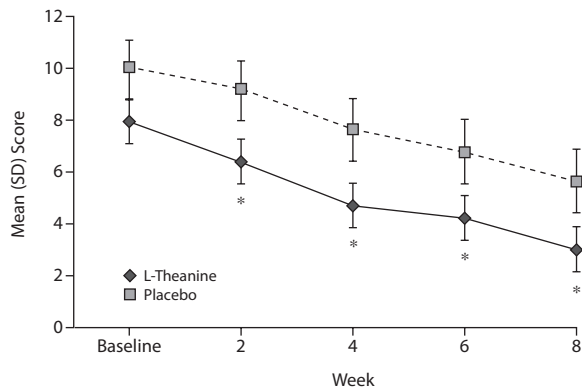
*P < .05; onset of improvement occurred in week 2.

scale) and positive and general psychopathology scores (assessed by the PANSS 3-dimensional model). It should be mentioned that the beneficial effect of L-theanine was noticed from the second week of treatment. According to the 5-factor model of the PANSS, L-theanine produced significant reduction in activation and positive factor scores compared to placebo (after the Bonferroni correction). The onset of the L-theanine amelioration effect was observed from second and sixth weeks, respectively. The effect sizes (Cohen d) for these changes were modest to moderate (0.09–0.39). No significant main effect for completers and noncompleters, as well as for interactions (treatment conditions by time), was found. Type (FGAs or SGAs) and daily dose of antipsychotics or diagnosis, did not influence between-group differences. Our findings regarding the ameliorative effect of L-theanine on anxiety are compatible with previous reports in which L-theanine showed some anxiolytic properties.[14,41–43] A few studies performed on healthy volunteers show that L-theanine increases α brain wave activity, which correlates with a perceived state of relaxation.[44,45] Moreover, L-theanine (200 mg) compared to alprazolam (1 mg/d) and placebo in healthy human subjects demonstrated a relaxing effect.[14] Accumulated evidence suggests that L-theanine ameliorates emotional distress,[42,45] subjective well-being,[46] and sleep quality.[47]

The second branch of the study suggests that L-theanine did not induce amelioration of negative and depressive symptoms, general functioning, extrapyramidal side effects, or cognitive and quality of life impairments during the study period. According to Hintikka and coworkers,[48] a positive association between low levels of depressive symptoms in the Finnish general population and daily tea drinking was found. The authors describe a 50% reduced risk of depression among tea drinkers. On the other hand, Shimbo and colleagues,[49] who screened tea drinkers, did not find any linkage between green tea consumption and mental health. Both studies were performed in healthy populations. Our results do not support the Finnish researchers' conclusions, although there are many biological active ingredients in

green tea, such as catechin, caffeine, tannin, flavonoid, and vitamin C. Juneja and colleagues[50] reported that L-theanine improves cognitive function, attention, and learning, as well as heightens mental acuity; however, our findings do not support these conclusions. This discrepancy may be explained by the fact that our study is based on schizophrenia patients, while these researchers performed their study on healthy subjects. The length of our study treatment was too short to observe changes of quality of life and cognitive improvement.

In the third branch, as hypothesized, L-theanine was found to be a safe and well-tolerated medication. Our results show that L-theanine did not produce any side effects.

Next, since 8 patients who dropped out during the first 2 weeks were excluded from statistical analysis, one methodological point (the true intention-to-treat analysis) should be mentioned here. The complex issues that arise in conducting and interpreting data from intention-to-treat analyses in studies with substantial levels of protocol violation (eg, attrition, noncompliance, or withdrawal of participants) have been widely discussed.[51–53] True intention-to-treat analyses are rare in reports of randomized clinical trials.[54] In practice, however, ad hoc methods such as LOCF imputation and complete-case analysis continue to be used.[55] Leucht and associates[56] reanalyzed a number of pivotal studies comparing SGAs and FGAs. These researchers applied 4 different models: LOCF, completer analysis, LOCF but excluding dropouts due to adverse events, and LOCF but excluding all dropouts with the exception of dropouts related to efficacy. Effect sizes expressed as standardized mean differences between SGAs and FGAs based on the 4 different analysis models were compared. Differences in overall results were not statistically significant irrespective of the model used.[56]

The mechanisms by which L-theanine might exert its antianxiety and antipsychotic effects have not been clearly elucidated in the scientific literature. Animal neurochemistry studies suggest that L-theanine increases brain GABA, 5-HT, and DA levels and that it has micromolar affinities for AMPA and NMDA receptors.[7] L-Theanine's chemical structure is similar to that of L-glutamate, suggesting that it is able to act as a GABA agonist, capable of increasing brain GABA levels. According to the classic dopaminergic theory of psychosis, increased levels of brain dopamine may cause a psychotic attack. Since our results demonstrate amelioration of psychotic symptoms due to L-theanine addition to antipsychotic drugs, in opposition to its ability to increase dopamine level, we cannot explain our results by the classical theory. There are other modern theories of schizophrenia that can provide an explanation to this contradiction.[57–59]

The specific mechanisms by which L-theanine exerts its neuroprotective action are just beginning to be studied and clarified. L-Theanine acts antagonistically against the stimulatory effects of caffeine on the nervous system.[16] Research on human volunteers has demonstrated that L-theanine creates a sense of relaxation within approximately 30–40 minutes after ingestion via at least 2 different mechanisms. First, this amino acid directly stimulates the production of

α brain waves in occipital, parietal, and frontal brain areas, creating a state of deep relaxation and mental alertness similar to that achieved through meditation. Second, L-theanine is involved in the formation of the inhibitory neurotransmitter, GABA. GABA, in its turn, influences the levels of 2 other neurotransmitters—dopamine and serotonin, which are the key to the relaxation effect.[18] Recent evidence indicates that, in addition to well-established antioxidant properties, L-theanine, together with other components of green tea, has a positive impact on cell survival/death genes and signal transduction pathways.[60] In the most recent publications there are some reports about L-theanine's neuroprotective properties against brain injury.[9,10] The positive results of our study may raise hopes and expectations that L-theanine may have neuroprotective ability in schizophrenia.

Limitations of this study include the relatively small sample size of patients and the relatively short duration of the study. Long-term, large-scale studies are required to obtain greater statistical significance and more confident clinical generalizations.

In conclusion, our results suggest that L-theanine augmentation to antipsychotic therapy can ameliorate anxiety and positive and general psychopathology symptoms in schizophrenia and schizoaffective disorder patients. Further long-term, randomized, controlled studies of L-theanine performed in bigger samples are needed in order to provide scientific justification for this clinical observation.

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