L-Arginine Add-On Treatment for Schizophrenia: A Randomized, Double-Blind, Placebo-Controlled, Crossover Study

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SUMMARY

Introduction: Current drug treatments for schizophrenia are only partially effective and combination/augmentation strategies are commonly used. Nitric Oxide (NO) may play a role in the pathophysiology of schizophrenia. L-arginine is the precursor of NO. In this study, we aimed to investigate whether L-arginine add-on to current medication might improve positive, negative, and depressive symptoms in schizophrenia/schizoaffective disorder patients in partial remission.

Method: The study was designed as a randomized, double-blind, placebo-controlled, crossover study of L-arginine 3 g b.i.d. as an add-on treatment to the patients' usual medication. Twelve patients diagnosed with schizophrenia/schizoaffective disorder were included. The duration of the treatment was 3 weeks, with a wash-out period of 7 days before alternation for the second arm. Psychopathology was assessed with the Positive and Negative Syndrome Scale (PANSS), the Calgary Depression Scale for Schizophrenia (CDSS), and the Clinical Global Impression (CGI) scales. The study was supported by Hacettepe University Scientific Research and Development Office (Project No: 011D0110101013) (Clinical Trials.gov Identifier: NCT02398279)

Results: Our analyses revealed that L-arginine 6 g/day add-on to usual treatment was not superior to placebo for positive, negative, and depressive symptoms associated with schizophrenia as assessed with PANSS, CDSS and CGI scales.

Conclusion: In our study, L-arginine did not seem to have an effect on schizophrenia symptoms. Studies with a larger sample size, with higher doses of L-arginine, and with a longer duration are needed for a definite conclusion.

Keywords: L-arginine, schizophrenia, nitric oxide, add-on therapy, treatment

INTRODUCTION

Schizophrenia is a disabling disorder that impairs social, occupational, and academic functioning and creates a burden for the society. Current treatment options include antipsychotic drugs that have limited impact on the disability. Even with optimum dose and duration of use, adequate response to antipsychotics is not achieved in 20-30% of schizophrenia patients (Conley and Buchanan 1997). Apart from the use of clozapine, the options are very limited in this subset of patients, and, in some, even clozapine use does not provide stability either due to the intolerance to the drug or the lack of efficacy (Geddes et al. 2000, Meltzer 2013).

The efficacy of current antipsychotic drugs relies mostly on their effects on dopamine and serotonin receptors. However, NMDA receptor dysfunction has been hypothesized to contribute to the disease process, and many potential agents were

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examined in clinical trials (Veerman et al. 2014). The common final outcome of these drugs is to modulate NMDA signaling, thus reversing the hypothesized hypofunction of the NMDA receptor. One clinical approach to target NMDA dysfunction in schizophrenia patients is to use glutamatergic drugs such as lamotrigine and topiramate or amino acids like glycine or D-cycloserine as adjuncts. There are positive and negative reports with these glutamate modulators in patient groups with different clinical characteristics (Heresco-Levy et al. 2005, Kremer et al. 2004, Vayisoglu et al. 2013).

Recently, many studies have reported differences in arginine metabolism in schizophrenia; for a detailed review, please check Liu et al.'s article (2016). Some studies suggested that alterations in arginine metabolism were associated with disease duration (Tomiya et al. 2007), while others found changes even in the first-episode patients (Zincir et al. 2014, Misiak et al. 2016). An increase in the levels of agmatine, a metabolite of L-arginine through arginine decarboxylase, was suggested as a potential biomarker (Uzbay et al. 2013). Furthermore, psychotropics were associated with changes in NO and L-arginine metabolism (Maia-de-Oliveira et al. 2012, Nonaka-Hashida et al. 2016). However, one must note that these changes were not reliably replicated across different studies (Jorgensen et al. 2015).

Nitric oxide is a neuromodulator affecting glutamatergic signaling in addition to the serotonergic and dopaminergic systems. NO is synthesized by the enzyme nitric oxide synthase (NOS), which utilizes L-arginine as the major substrate (Boger 2014). Preclinical studies suggest a useful role for the modulation of NO signaling in models that mimic NMDA receptor hypofunction. Bujas-Bobanovic et al. demonstrated in mice that sodium nitroprusside, an NO donor, corrected the behavioral alterations caused by a NOS inhibitor, N(G)-nitro-L-arginine methyl ester, as well as PCP-associated c-fos expression (Bujas-Bobanovic et al. 2000a, Bujas-Bobanovic et al. 2000b). On the other hand, another NOS inhibitor, N(omega)-propyl-arginine, improved PCP-associated locomotor activity and corrected cognitive deficits (Klamer et al. 2004). Similarly, NOS inhibitors recovered some schizophrenia-associated phenotypes in rodents (Issy et al. 2011). In addition to these contradictory findings of NO signaling on glutamatergic transmission, intact NO functioning was deemed necessary for PCP-associated impairment since PCP treated *nNOS* KO mice did not display behavioral changes (Bird et al. 2001, Klamer et al. 2005). Nitric oxide signaling was also altered in animal models that target different aspects of schizophrenia (Kajitani et al. 2010, Ribeiro et al. 2013). These findings suggest the involvement of nitric oxide-related pathways in schizophrenia pathophysiology, thus making nitric oxide pathways a potential therapeutic target, although the underlying mechanisms are yet to be determined.

The effects of antipsychotics on NO levels are variable. A systematic review on plasma/ serum NO levels in schizophrenia patients suggested an increase in the levels with the use of antipsychotics (Maia-de-Oliveira et al. 2012). In experimental models, however, different antipsychotics, including haloperidol, risperidone, and clozapine attenuated NO levels in both plasma and brain tissue samples (Bringas et al. 2012, Negrete-Diaz et al. 2010, Shioda et al. 2012). Therefore, in addition to its possible pathogenic effects, NO signaling may also take part in the mechanism of effect of antipsychotics.

L-arginine is a conditionally essential amino acid that is the precursor of NO. L-arginine is a part of a daily diet and was shown not to have adverse effects at doses of 3-8 mg/day in the cardiovascular literature (Boger 2007, Alizadeh et al. 2012). With a regular diet, L-arginine plasma levels were found to be (mean±SD) 72.4±6.7 μmol/L in young females and 81.6±7.3 μmol/L in young males (Boger 2007). The maximum dose of L-arginine in studies using supplements was 30 g parenterally or 15 g PO. Bode-Böger et al. (1998) found that the plasma level of L-arginine was 310±152 μmol/L with 6 g PO and 822± 59 μmol/L with 6 g parenterally. In the same study, 30 g daily parenteral L-arginine resulted in L-arginine levels of 6223± 407 μmol/L (Bode-Boger et al. 1998). In another study (Walker et al. 2001), two weeks of 15 g PO daily L-arginine increased the plasma levels from 80±2 to 117±4 μmol/l. In addition to its role in protein synthesis, L-arginine is converted into L-citrulline and NO via NOS, as well as to bioactive molecules that take part in glutamate and GABA synthesis such as L-ornithine and urea via arginase. Furthermore, L-arginine is converted into agmatine via arginine decarboxylase, which is the endogenous inhibitor of NO (Galea et al. 1996) and a putative neurotransmitter taking part in schizophrenia pathogenesis (Uzbay et al. 2013). Utilizing L-arginine to stimulate NO production could reverse the functional effects in the case of NMDA dysfunction. Since NMDAR hypofunction is associated not only with positive symptoms but also with negative and cognitive symptoms, we hypothesized that L-arginine may have beneficial effects on diverse dimensions of schizophrenia. In this study, we aimed to determine whether L-arginine would be effective in reducing different domains of psychopathology in schizophrenia patients when used as an add-on treatment to the usual therapy.

METHOD

Study Site and Participants

The study was conducted at Hacettepe University, Faculty of Medicine, Department of Psychiatry, Ankara, Turkey. The study was approved by Hacettepe University Local Ethics Committee (LUT 10/72). Written informed consent was obtained from all participants and their caregivers.

Patients with a diagnosis of schizophrenia/schizoaffective disorder according to DSM-IV (American Psychiatric Association, 2000) were included in the study. Other inclusion criteria were age between 18 and 65 years, stable psychiatric condition, i.e., Clinical Global Impression Score of 4 or above with the same dose of antipsychotic in the previous two months, being eligible for outpatient visits (symptoms may continue but not regarded as necessary for hospitalization by the responsible physician), and a lack of diagnosis of alcohol/substance use disorder in the last three months. Presence of an uncontrolled medical illness (renal failure, uncontrolled diabetes, hepatic failure, cardiac diseases, low- or high-blood pressure), pregnancy and breastfeeding were accepted as the exclusion criteria. Six out of 18 patients evaluated were excluded, five due to chronic medical illnesses and one due to active alcohol/substance use.

Study Design and Drug Preparation

The study was designed as a 7-week-long, randomized, double-blind, crossover and placebo-controlled trial. Patients were divided into two groups; the first group received 3 weeks of 6 g/d L-arginine followed by placebo, while the second group started with placebo and then continued with 6 g/day L-arginine. There was a one-week washout period between the treatment phases. For the sake of simplicity, the first group, which began with L-arginine, will be called 'L-arginine initiated' and the second group, which began with placebo, will be called 'Placebo-initiated'.

Capsules containing 500 mg of L-arginine were available as commercial products (Solgar Inc.). Placebo capsules were prepared by the Department of Pharmaceutical Technology, Hacettepe University. The study drug was provided weekly to the participants by the lead author. The assessments were conducted by the first and second authors who were residents of psychiatry trained for the study under the supervision of the corresponding senior author.

ASSESSMENT MEASURES

Positive and Negative Syndrome Scale (PANSS)

Positive and Negative Syndrome Scale (PANSS) was developed in order to assess positive and negative symptoms in schizophrenia (Kay et al. 1987). PANSS is a semi-structured interview scale and comprises 30 items, the severity of each graded on a 7-point scale. Out of 30 items, 7 belong to the Positive Syndrome, 7 to the Negative Syndrome, and the remaining 16 to the General Psychopathology Subscales. The Subscales and PANSS scores can be obtained separately. The scale was translated to Turkish, and validity and reliability studies were conducted (Kostakoğlu et al. 1999). In addition to the subscales and total score, in subsequent studies, a PANSS-Depression Cluster was identified comprising PANSS General Psychopathology Subscale G1 (Somatic worry), G2 (Anxiety), G3 (Feelings of guilt), and G6 (Depression) (Kay and Sevy 1990, Tollefson et al. 1999). In the current study, we evaluated psychopathology and symptom severity using PANSS.

Clinical Global Impression Scale -CGI

Clinical Global Impression Scale (CGI) was developed to assess the positive and negative changes during follow-up of the patients. The clinician rates the severity of the disease between 1 and 7 points according to his/her impression (1= normal/not at all ill, 2=borderline ill, 3=mildly ill, 4=moderately ill, 5=markedly ill, 6=severely ill, 7=among the most extremely ill patients) (Beneke and Rasmus 1992). We used CGI-S to determine the severity of the illness during the study period.

Calgary Depression Scale for Schizophrenia (CDSS)

Calgary Depression Scale for Schizophrenia (CDSS) is a semi-structured scale designed to assess the level of depression in schizophrenia patients and differentiate from extrapyramidal side effects and psychosis (Addington et al. 1990). The scale is composed of 9 items scoring depression, hopelessness, self-depreciation, guilty ideas of reference, pathological guilt, morning depression, early awakening, suicide, and observed depression. Each item is scored from 0 to 3 (0=absent, 1=mild, 2=moderate, 3=severe), and total scores are obtained. Validity and reliability studies for the Turkish version exist (Aydemir et al. 2000). The scale was used to assess depression in our study.

UKU Side Effect Rating Scale (UKU)

UKU (Udvalg for Kliniske Undersogelser) Side Effect Rating Scale was generated to assess side effects in people using antipsychotic drugs (Lingjaerde et al. 1987). The scale is composed of 48 items evaluating mental, neurological, autonomic, and other side effects. Side effects occurring in the last 72 hours are assessed, and the effects are scored from 0 to 3 based on the severity. Each item can be rated within 4 degrees, with '0' denoting 'no side effects' and '3' 'severe side effects'. The scale was used to evaluate treatment safety in the study.

Abnormal Involuntary Movement Scale (AIMS)

Abnormal Involuntary Movement Scale (AIMS) was developed by the American National Institute of Mental Health Psychopharmacology Research Branch in 1976 to assess the level of dyskinesia in detail in neuroleptic receiving patients. The scale is composed of twelve items. The first four items assess oro-facial dyskinesias, and the 5th to 7th items assess limb and axial dyskinesias. The 9th and 10th items evaluate the severity, functional consequences, and disability caused by

the dyskinesias, and the 11th and 12th items evaluate the existence of dental implants and related-problems. Most items have a 5-level graded scoring system. The scale was used to evaluate treatment safety in the study.

Efficacy Measures

The primary outcome measure for efficacy was the change in the Positive and Negative Syndrome Scale scores (PANSS) (Kay et al. 1987, Kostakoğlu et al. 1999). Secondary outcome measures were the change in depressive symptoms as assessed by CDSS (Addington et al. 1990, Aydemir et al. 2000) and the depressive cluster of PANSS; and the change in the clinical severity of symptoms as assessed with Clinical Global Impression – Severity scale (CGI-S) (Busner and Targum 2007). The assessments were performed at baseline, at the end of the first treatment phase (3rd week), at the beginning of the second treatment phase (second baseline, 5th week), and at the end of second treatment phase (7th week).

Safety Measures

Physical examination was performed and vital signs were evaluated at the first visit. Body weight, BMI, Complete Blood Count, Liver Function Tests (LFT), Renal Function Tests (RFT), Thyroid Function Tests, lipid profile including total cholesterol, HDL-C, LDL-C and triglycerides, and full blood chemistry with electrolytes were measured. Electrocardiogram (ECG) was obtained at the beginning and at the end of the study. UKU Side Effect Rating Scale (UKU) and Abnormal Involuntary Movement Scale were assessed at the first visit and at the 3rd, 5th and 7th weeks.

Data Analysis

Statistical analyses were performed using SPSS for Windows, v.15.0. Categorical variables were expressed as numbers and percentages, and numeric variables were expressed as means and standard deviations. Mann–Whitney U test was used to assess differences in categorical variables between the groups. Differences between the visits were compared using the Friedman test; if there were differences between two or more visits, Wilcoxon test was used. The level of significance was accepted as $p<0.05$.

RESULTS

Sample Characteristics

The sociodemographic characteristics of the patients are presented in Table 1. The mean age for the whole group was 29.00±5.95 years. All but one patient was diagnosed with schizophrenia; the other patient was diagnosed with schizoaffective disorder. Mean age of onset was 21.00±4.80 years.

Table 1. Sociodemographic characteristics.

	Whole group	L-A/P	P/L-A	p
n	12	6	6	
Age (mean ± SD)	29±5.95	32.5±5.0	25.5±4.8	0.07
Gender (F:M)	5:7	2:4	3:3	>0.05
Marital status				>0.05
Single	12	6	6	
Married	0	0	0	
Divorced/ Widowed	0	0	0	
Education				>0.05
0-8y	6	3	3	
>8y	6	3	3	
Employment status				>0.05
Employed	4	2	2	
Not-employed	8	4	4	
Diagnoses				>0.05
Schizophrenia	11	6	5	
Schizoaffective Disorder	1	0	1	
Age of onset (mean±SD)	21±4.80	24±4.2	17±2.9	0.03

L-A/P group started with L-arginine and continued with placebo in the second phase, and P/L-A group started with placebo and continued with L-arginine in the second phase. P values represent significance levels of comparisons between L-A/P and P/L-A groups. F: Female, M: Male, y denotes year.

Mean duration of illness was 8.10±3.69 years. The sociodemographic and baseline characteristics of L-A/P and P-L/A, such as age, gender, marital status, education levels, and age of onset and the illness duration were compared. Age of onset in P-L/A was significantly lower than L-P/A (Table 1). PANSS total scores were not different, 64.5 (46-87) in L-A/P and 58 (49-98) in P-L/A (p=0.39) (Table 2). A total of six patients were using clozapine. Four of the six patients were prescribed solely clozapine, one patient clozapine plus aripiprazole, and one patient clozapine plus fluphenazine decanoate and chlorpromazine. For the remaining patients, three were on olanzapine, one was using risperidone, one was using paliperidone, and one was using amisulpride. The mean dose of antipsychotics adjusted for chlorpromazine was 545±381 mg/d (Gardner et al. 2010).

Efficacy of L-Arginine Add-on Therapy

The severity of illness measured by PANSS, CDSS and CGI-S were not different at baseline between the two treatment groups. No significant differences were observed between the treatment groups in PANSS Total, Positive, Negative, and General Psychopathology scores in any of the visits (Table 2, the percent changes in PANSS scores were displayed at Figure

Table 2. Effects of L-arginine

Visit	PANSS Positive Subscale		PANSS Negative Subscale		PANSS General Psychopathology Subscale		PANSS Total Score		CGI		CDSS	
	L-A/P	P/L-A	L-A/P	P/L-A	L-A/P	P/L-A	L-A/P	P/L-A	L-A/P*	P/L-A	L-A/P	P/L-A
Wk 0	16	16.5	17	16	32	28	64.5	58	4	4	5	3
	(12-26)	(14-26)	(13-19)	(11-25)	(21-42)	(24-47)	(46-87)	(49-98)	(4-6)	(4-6)	(1-11)	(1-7)
Wk 3	16	14	16.5	13.5	30	24	62.5	53	4.5	4	4.5	1,5
	(11-24)	(11-25)	(10-22)	(8-25)	(19-40)	(19-42)	(40-86)	(40-92)	(4-6)	(3-6)	(0-11)	(0-6)
Wk 4	15.5	14.5	17.5	14	30.5	25	61.5	53.5	4	4	6	3,5
	(11-25)	(10-27)	(9-19)	(9-25)	(21-40)	(20-45)	(41-84)	(39-97)	(3-6)	(3-6)	(0-10)	(0-7)
Wk 7	16	15	18	13.5	31	26	65	57.5	4	4	2.5	4,5
	(11-24)	(11-27)	(9-22)	(12-23)	(20-38)	(20-43)	(40-84)	(46-93)	(3-5)	(3-6)	(0-10)	(1-8)

CGI: Clinical Global Impression, CDSS: Calgary Depression in Schizophrenia Scale

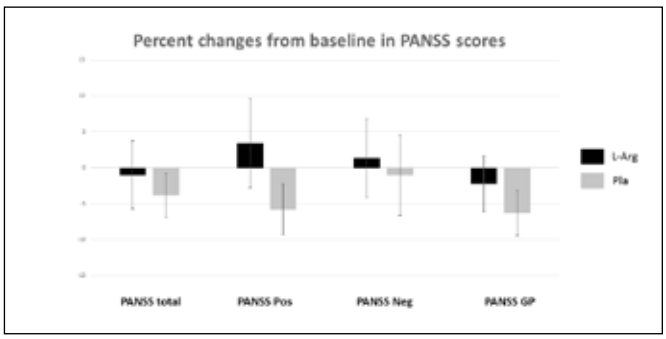

Figure 1. PANSS pos: PANSS positive subscale scores, PANSS neg: PANSS negative subscale scores, PANSS GP: PANSS general psychopathology scores. L-A: L-arginine, Pla: Placebo.

1). L-arginine did not have an impact on CDSS and PANSS depressive cluster scores. Similarly, albeit there was a significant difference between the CGI-S scores within the visits of L-A/P group (p=0.036), this difference was not evident in P/L-A group, and no post-hoc difference was observed in L-A/P group either.

Treatment Safety

All participants completed the study. There were no serious adverse events requiring treatment. There were no significant differences between the treatment groups regarding the UKU and AIMS assessments, vital signs, weight, ECG, and laboratory measures at the beginning and end of each treatment.

Analyses of Clozapine-Treated Patients

Since the reason for initiating clozapine is primarily treatment resistance, and response to new medications might differ in these patients, we also conducted our analyses in clozapine-treated patients. Due to the low numbers of patients receiving clozapine (a total of 6), we grouped the data collected and then compared the effects of placebo and L-arginine. No differences in psychopathology were observed.

DISCUSSION

In this study, we examined the effects of L-arginine add-on to usual treatment in a randomized, placebo-controlled, double-blind crossover study. L-arginine was safe and well-tolerated. We were not able to display any effect of 6 g/d L-arginine PO on positive, negative, and depressive symptoms in schizophrenia. Since clozapine-treated patients might form a different group than the others in terms of treatment response, we also conducted a separate analysis of the clozapine-treated patients, and no difference was found in the effectiveness of L-arginine in this group of patients either.

This study, to our knowledge, is the first to evaluate the effects of L-arginine in schizophrenia. Previous studies that aimed to modulate the glutamatergic system mainly targeted the NMDAR, either with direct regulation via glycine, serine, D-cycloserine and sarcosine or indirectly with lamotrigine and topiramate. With this study, however, we undertook a different approach, aiming to control the putative hyperglutamatergic state associated with NMDAR hypofunction by using a precursor of one of its modulators, NO, which has the potential to be a novel pharmacological target.

Other than addressing a new therapeutic mechanism for schizophrenia, L-arginine has unique advantages in terms of its intrinsic properties. First, L-arginine is not a drug, but a complementary amino acid that is a part of a normal diet in most cultures. Second, L-arginine use may be beneficial for the cardiovascular system; in particular, L-arginine is considered as an antioxidant agent and improves endothelial function in coronary heart disease (Tousoulis et al. 2007). This point may be particularly important given the high rates of metabolic syndrome in schizophrenia and mortality associated with ischemic heart disease (Schoepf et al. 2014, Yazici et al. 2011).

We did not observe a significant change in any subgroup of the PANSS scores as our primary outcome measure. In addition, the secondary outcomes defined as depression scores did not change with L-arginine administration. The negative findings may be due to the small sample size. Our study was the first to utilize L-arginine for this indication. Therefore, it was not possible to perform a power analysis using an estimate of effect size to determine the minimum sample size. In addition, the logistic constraints on funding and time had determining effects on the sample size and the duration of the study. In this study, the group as a whole comprised 12 individuals. In order to overcome the low sample size, we decided to conduct a crossover design that allowed us to use a placebo control group. However, it is still possible that with a larger sample, the putative effect of L-arginine on psychopathology might be evident. The second methodological limitation was the heterogeneous nature of the group in terms of disease severity and diagnoses. The participant with schizoaffective disorder might be expected to respond differently to the effects of L-arginine. In addition, 50% of the patients were using clozapine, and 2 out of 12 were even on augmenting agents in addition to clozapine. Clinical efficacy of a new therapeutic approach may be different in treatment-resistant and also clozapine-resistant patients compared to non-resistant cases. Although our analyses revealed similar results in clozapine-using patients and patients on other antipsychotics, it is possible that these secondary analyses further impeded the sample size and covered putative positive effects of L-arginine augmentation. In addition, glutamatergic modulators are hypothesized to display their effects more on the negative symptoms (although contradicting results exist in the literature) (Hashimoto et al. 2013, Sommer et al. 2012, Umbricht et al. 2014), and the efficacy of L-arginine may be different on different patient groups in terms of the severity of symptom dimensions. The possible effects might have been elicited with a more selected sample of patients, i.e., patients with more prominent negative or depressive symptoms.

Since this is the first trial of L-arginine in psychiatric disorders and schizophrenia in particular, we were not able to determine a trial dose based on any previous experience. Therefore, the dose was selected based on the doses tried in the cardiovascular literature, in which 6 g/day was proven to be safe. However, we do not know whether the dose selected was sufficient for L-arginine to demonstrate its effects in the CNS. In fact, we were not able to directly measure CSF L-arginine levels or estimate indirectly with a functional method. Thus, it is possible that higher doses of L-arginine are needed to elicit a positive response in schizophrenia patients.

Lastly, three weeks might not be adequate to demonstrate the possible effects. Efficacy studies in schizophrenia generally include longer trial periods (Kulkarni et al. 2016, O'Donnell et al. 2016, Ritsner et al. 2014). Therefore, one might argue that the putative effects of L-arginine might not be evident during the trial period, and a longer duration is needed to observe the effects.

In conclusion, we were not able to display a positive effect of L-arginine on the measures of psychopathology. This lack of significance may be due to several reasons including the sample size, design and the dose applied. Regardless, the supplement at the current dose was safe. Studies with a larger sample size, in patient groups with different characteristics, and with higher doses of L-arginine are needed to elucidate putative effects of the supplement.

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