α-Lipoic Acid as Adjunctive Treatment for Schizophrenia

An Open-Label Trial

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Abstract:

Purpose/Background: Accumulating evidence suggests an involvement of oxidative stress in the pathophysiology of schizophrenia. This offers a hypothesis-derived therapeutic approach to hinder oxidative damage and its clinical sequelae. α-Lipoic acid (ALA) is a powerful natural antioxidant indicated to treat diabetic neuropathy.

Methods/Procedures: In this pilot investigation, we administered ALA (100 mg/d) for 4 months, as an adjunct to antipsychotic medication, to 10 patients with schizophrenia.

Findings/Results: We found robust improvement in measures of psychopathology (63.9% reduction in Brief Psychiatric Rating Scale scores), neurocognitive parameters, extrapyramidal symptoms, and decreased lipid peroxidation.

Implications/Conclusions: If larger, double-blind, placebo-controlled studies confirm these preliminary findings, ALA could prove useful as adjunctive therapy for schizophrenia.

Key Words: schizophrenia, α-lipoic acid, antioxidant, drug repurposing, neurocognitive parameters, extrapyramidal symptoms

(*J Clin Psychopharmacol* 2017;37: 697–701)

There is compelling evidence for oxidative stress and inflammatory alterations in schizophrenia.[1] Several studies have reported low endogenous antioxidant levels and signs of oxidative stress in patients with this disorder.[2–4] The discovery of impaired antioxidant defense system and inflammatory abnormalities in schizophrenia offers a therapeutic approach to hinder oxidative damage, inflammation, and its clinical sequelae.[5,6]

α-Lipoic acid (ALA), also known as thioctic acid, is a naturally occurring compound, synthesized in the mitochondria, with an expanding list of clinical applications. Most notably, it is used to treat diabetic neuropathic pain.[7] α-Lipoic acid and its reduced form, dihydrolipoic acid, are powerful antioxidants[8] with anti-inflammatory effects.[9]

A preclinical study showed that ALA alone and ALA combined with clozapine reverse schizophrenia-like symptoms and pro-oxidant changes induced by ketamine in mice.[10] Before the advent of antipsychotics, 2 studies found that low doses of ALA relieved symptoms in patients with schizophrenia.[11,12] More recently, clinical studies did not observe improvement in psychopathology with a daily 300 mg[13] or 1200 mg dose of ALA,[14] raising the possibility of a low-dose therapeutic window for ALA in schizophrenia.[15] Here we report the results of an open-label trial of ALA (100 mg/d) as an adjuvant to antipsychotics therapy in schizophrenia.

METHODS

We conducted a 4-month open-label trial of ALA at dosages of 100 mg/d added to ongoing antipsychotics in patients (ages 18–60 years) with stable chronic schizophrenia. Patients were not in the acute phase of the disease and remained on stable doses of antipsychotic drugs for at least a year before the beginning of the trial. The institutional review board approved the study protocol. All participants gave written informed consent before study enrollment. A total of 12 patients enrolled in the study. The diagnosis was confirmed using the Structured Clinical Interview for DSM-IV. Exclusion criteria were pregnancy, neurological disease, actual substance use, brain tumor, uncontrolled endocrine and cardiac disease, and severe systemic disease. We evaluated patients' psychopathological state using the 18-item Brief Psychiatric Rating Scale (BPRS)[16] and drug-related extrapyramidal symptoms using the 10-item Simpson-Angus Extrapyramidal Symptoms Scale[17] at baseline and monthly until the end of the study (5 visits). Response was defined as 25% or more reduction in BPRS total score within 4 months.[18]

At visits 1 and 5, we performed neuropsychological assessment, consisting of the following tests: Trail Making Test,[19] Block Corsi Test,[20] Subtest Digit Span,[21] Category (Animal) Fluency and Controlled Oral Word Association Test, COWA (FAS test),[22] and Rey Auditory Verbal Learning Test,[23] as well as measures of abdominal circumference, body mass index (BMI) calculation, and collection of peripheral blood sample (10 mL). Complete blood count, plasma levels of alanine aminotransferase (ALT) and aspartate aminotransferase (AST), glycohemoglobin (HbA1c), folic acid, vitamin B_{12}, ultrasensitive C-reactive protein (hs-CRP), plasma

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Received May 28, 2017; accepted after revision September 6, 2017.

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Supplemental digital content is available for this article. Direct URL citation appears in the printed text and is provided in the HTML and PDF versions of this article on the journal's Web site (www.psychopharmacology.com).

ISSN: 0271-0749

DOI: 10.1097/JCP.0000000000000800

TABLE 1. Sample Characteristics

Sex (male/female)	6:4
Age, y	38.5 (7.26)
Years of education	6.67 (2.74)
Years of disease	18.70 (7.33)
Chlorpromazine-equivalent dose, mg/d	646.25 (431.09)

Values are given as the mean (SD).

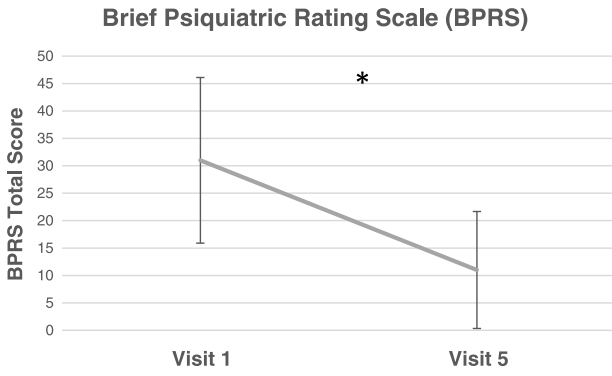

FIGURE 1. Mean BPRS total score at visits 1 and 5. Error bars indicate ±1 SD. *P = 0.000004 (paired-sample t test).

glutathione (GSH),[24] nitrite,[25] thiobarbituric acid–reactive substances (TBARS),[26] interleukins (ILs) 1β and 4, interferon γ (IFN-γ; R&D systems, Minneapolis, MN), and indoleamine 2,3-dioxygenase (IDO) activity[27] were determined.

Statistical analysis was performed using SPSS version 20.0, conducting Mann-Whitney U test or Student t test, as appropriate. Descriptive data were expressed as mean ± SD or as median and interquartile interval (25%–75%). P values of 0.05 or less, 2-tailed, were considered significant. We used 2-way repeated-measures analysis of variance (ANOVA) to test for improvements on the Rey Auditory Verbal Learning Test.

RESULTS

Two patients dropped out of the trial after enrollment. One of them alleged lack of time to participate in the follow-up, and the other one developed persecutory delusions involving the medication and refused to take the study drug. Ten patients completed the study. Sample characteristics and the mean chlorpromazine equivalent dose of antipsychotic agents are displayed in Table 1. Patients continued to receive stable doses of concomitant antipsychotic medications, which are listed in the Supplementary Material, Supplemental Digital Content 1, http://links.lww.com/JCP/A485. No adverse effects were reported during the study period.

All patients responded to the adjuvant treatment with ALA. Mean BPRS total scores are depicted in Figure 1. We observed 63.9% improvement from baseline. Paired-sample t-test revealed a significant difference in BPRS total scores between visits 1 and 5 (t = 9.887, P = 0.000004). The reduction in BPRS scores occurred in all symptom domains[28] (Table 2). All patients showed a decrement of at least 25% in negative/disorganization symptoms; 9 patients, in excitement; 8 patients, in depressive symptoms; and 7 patients, in positive symptoms. There was also a significant reduction of extrapyramidal symptoms, as measured by the Simpson-Angus Extrapyramidal Symptoms Scale (visit 1: median = 5, 25–75% = 4–115; visit 5: median = 2, 25–75% = 0.75–2.75; Wilcoxon signed rank test, P = 0.008).

We found a significant improvement in all neurocognitive tests (see Table 3), except for the Category (Animal) Fluency and the FAS test, which are measures of verbal fluency. Figure 2 displays patients' scores on the RAVL test, which consists of 8 different stages in which subjects repeat a list of words (Rey 1–5), are distracted by another list (Rey 6), recall the first list (Rey 7), and recognize words from a bigger list (Rey 8). A 2-way repeated-measures ANOVA revealed a main effect of *test stage* ($F_{7,94}$, P = 0.000). There was also a main effect of *time* ($F_{1,54.53}$, P = 0.00008), indicating that patients' scores were significantly higher after 4-month adjuvant treatment with ALA, and a *test stage* × *time* interaction ($F_{7,4.11}$, P = 0.001), which points to a greater effect of treatment on retention of information than on immediate recall.

Comparing values at baseline and after 4-month of adjunctive treatment with ALA, we did not find significant difference in abdominal circumference, BMI, complete blood count, levels of ALT and AST, HbA1c, vitamin B_{12}, hs-CRP, GSH, nitrite, IL-1β, IL-4, IFN, and IDO activity (Table 4). We found a significant reduction of TBARS, which are byproducts of lipid peroxidation (t = 4.90, P = 0.002; Fig. 3) and of folic acid (t = 2.36, P = 0.042; Table 3).

DISCUSSION

In this pilot investigation, we administered ALA for 4 months as an adjunct to antipsychotic medication to 10 patients with schizophrenia. At the end of the trial, we found robust improvement in measures of psychopathology (63.9% improvement from BPRS baseline scores), neurocognitive parameters, extrapyramidal symptoms, and a decrease in lipid peroxidation.

An open-label trial has the potential to introduce bias into the results. The use of objective measures such as neurocognitive testing and oxidative and inflammatory parameters partly compensates this limitation of our study.[29] Randomized, double-blind, placebo-controlled studies with larger samples should be encouraged as

TABLE 2. Mean BPRS Dimension Scores Before and After ALA Adjuvant Treatment

BPRS Symptom Dimension	Visit 1	Visit 5	Test Statistics
Negative/disorganization symptoms (emotional withdrawal, disorientation, blunted affect, mannerisms/posturing, and conceptual disorganization)	10.30 (3.06)	3.20 (2.94)	t = 10.05, P = 0.000003*
Excitement (excitement, hostility, tension, grandiosity, and uncooperativeness)	8.50 (4.62)	2.20 (2.04)	t = 5.24, P = 0.001*
Depressive Symptoms (depressive mood, guilt feelings, and motor retardation)	6.80 (4.29)	3.60 (3.09)	t = 4.59, P = 0.001*
Positive symptoms (unusual thought content, suspiciousness, and hallucinatory behavior)	6.70 (6.02)	3.20 (4.36)	t = 2.82, P = 0.020*

Values are given as the mean (SD), with 2-tailed P values.
*$P \leq 0.05$.

TABLE 3. Neuropsychological Test Results

Test	Visit 1	Visit 5	Test Statistics
Trail Making Test			
Part A			
Time, s	109.67 (68.08)*	69.89 (36.18)*	$t_8 = 2.884$, $P = 0.020^{\dagger}$
Errors	3 (0–4.5)‡	0 (0–1.5)‡	Wilcoxon signed rank test, $P = 0.066$
Part B			
Time, s	231.78 (119.14)*	173.11 (87.62)*	$t_8 = 3.856$, $P = 0.005$*
Errors	4.11 (3.41)*	2.22 (2.05)*	$t_8 = 3.507$, $P = 0.008^{\dagger}$
Block Corsi Test	9.00 (2.65)*	14.67 (4.63)*	$t_8 = -4.808$, $P = 0.001^{\dagger}$
Subtest Digit Span	8.56 (2.29)‡	14.11 (2.76)‡	$t_8 = -6.934$, $P = 0.0001^{\dagger}$
Category (Animal) Fluency	11.89 (2.15)*	14.22 (3.53)*	$t_8 = -2.135$, $P = 0.065$
FAS test	14.44 (8.94)*	16.67 (7.94)*	$t_8 = -1.769$, $P = 0.115$

*Mean (SD).
†$P \leq 0.05$.
‡Median (interquartile interval, 25%–75%).

a next step to further elucidate the clinical benefit of ALA treatment in schizophrenia.

Our results are in line with 2 studies conducted in the 1950s, before the use of antipsychotic medication became widespread,[11,12] which found that ALA relieved symptoms in at least half of the patients with schizophrenia. Importantly, 2 of 3 patients who first showed improvement at the lower dose (100 mg) deteriorated when given a higher dose (200 mg).[12] More recently, a daily 300-mg[13] or 1200-mg dose of ALA[14,30] did not improve psychopathology in schizophrenia. There were no adverse effects reported with the high-dose ALA, but no beneficial changes in psychiatric symptoms either. Taken together, these previous results suggest a low-dose therapeutic window for ALA in the treatment of schizophrenia,[15] which might explain the clinical improvement observed here using a 100-mg daily dose.

In this pilot investigation, there was a significant increment in several neuropsychological tests, which provides objective evidence of patients' improvement in visual search, attention, mental flexibility, spatial working memory, semantic knowledge, verbal learning, retention of information, and recognition, after ALA adjuvant treatment. Patients' increase in verbal fluency (Category (Animal) Fluency and the FAS test) did not reach statistical significance.

In the present study, adjunctive treatment with ALA reduced patients' extrapyramidal symptoms. Accordingly, preclinical studies showed that ALA reverses haloperidol-induced DRD2 up-regulation in human neuroblastoma cells[31] and protects against haloperidol-induced oxidative damage in rat brain.[32] Our findings corroborate the hypothesis of ALA as a therapeutic agent to manage adverse effects related to the use of first-generation antipsychotics.

α-Lipoic acid as adjunctive treatment led to a significant reduction of plasma TBARS which have been previously reported as being in higher levels in patients with schizophrenia.[33] Vidovic and colleagues[34] demonstrated that 500 mg of ALA/d reduces the levels of TBARS in healthy subjects, but not in patients with schizophrenia. Again, the low-dose therapeutic window for ALA might explain the difference in outcomes. We did not observe changes in inflammatory parameters, probably because patients were using atypical antipsychotic drugs, which present anti-inflammatory effects.[35]

It has been shown that folic acid can scavenge and maintain ALA-protecting effects.[36] In our study, ALA adjuvant treatment

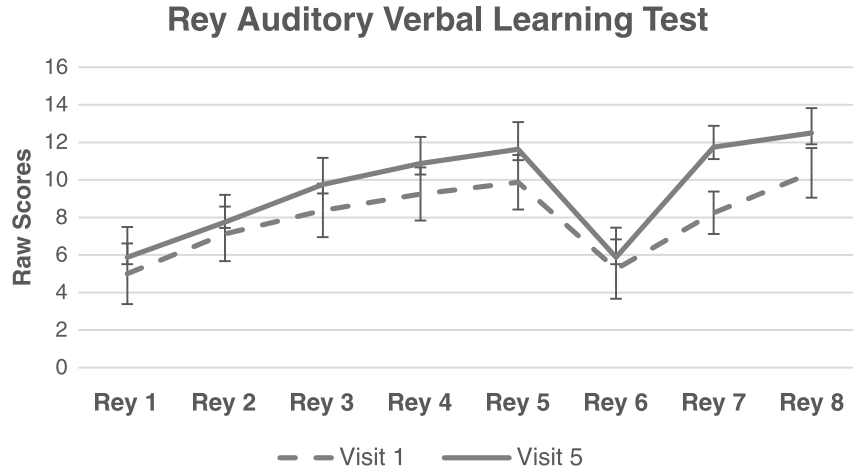

FIGURE 2. Patients' mean scores on the Rey Auditory Verbal Learning Test at visits 1 and 5. Error bars indicate ±1 SD. There was a main effect of test stage and of time, as well as a test stage × time interaction (2-way ANOVA).

TABLE 4. Abdominal Circumference, BMI, Laboratory Parameters, and Oxidative and Inflammatory Markers

	Visit 1	Visit 5	Test Statistics With 2-Tailed *P* Values
AC, cm	101.10 (19.25)	100.80 (18.56)	$t_9 = 0.217$, $P = 0.833$
BMI, kg/m^2	29.10 (7.69)	29.38 (7.33)	$t_9 = 0.712$, $P = 0.495$
Hb, g/dL	14.73 (1.15)*	14.31 (0.53)*	$t_9 = 1.294$, $P = 0.228$
Ht, %	43.84 (3.11)*	42.92 (2.36)*	$t_9 = 1.289$, $P = 0.229$
WBC, /μL	6950 (1970.87)*	7280 (2048.74)*	$t_9 = -0.839$, $P = 0.423$
NC, /μL	4138.90 (1259.85)*	4430.60 (1247.37)*	$t_9 = -0.741$, $P = 0.478$
PC, /μL	262,410 (115,173.65)*	200,520 (97,320.74)*	$t_9 = 1.336$, $P = 0.214$
ALT, U/L	31 (11.26)*	37.30 (18)*	$t_9 = -1.561$, $P = 0.153$
AST, U/L	31.10 (6.92)*	36.30 (9.77)*	$t_9 = -1.153$, $P = 0.279$
HbA1c, %	4.45 (0.61)*	4.66 (0.57)*	$t_9 = -1082$, $P = 0.307$
Folic acid, ng/mL	7.49 (2.3)*	5.50 (2.72)*	$t_9 = 2.362$, $P = 0.042$‡
Vitamin B_{12}, pg/mL	387.51 (135.69)*	364.64 (169.12)*	$t_9 = 0.671$, $P = 0.519$
hs-CRP, mg/dL	0.631 (0.672)*	0.593 (0.560)*	$t_9 = 0.197$, $P = 0.848$
GSH, ng/mL	31.56 (35.97–40.75)†	24.81 (22.25–28.88)†	Wilcoxon signed rank test, $P = 0.203$
Nitrite, nM/mL	1.44 (1.06)*	1.63 (0.84)*	$t_7 = -2.030$, $P = 0.098$
TBARS, mmol of (MDA)/mL	262.80 (48.90)*	195.77 (47.92)*	$t_7 = 4.905$, $P = 0.002$‡
IL-1β, pg/mL	42.88 (37.71)*	44.87 (37.74)*	$t_6 = -0.219$, $P = 0.834$
IL-4, pg/mL	88.74 (49.41)*	84.38 (52.92)*	$t_6 = 0.312$, $P = 0.765$
IFN-γ, pg/mL	26.01 (8.78)*	25.57 (7.43)*	$t_7 = 0.294$, $P = 0.777$
IDO activity, U IDO min^{-1} mg^{-1}	15.75 (2.46)*	21.74 (10.46)*	$t_7 = -1.561$, $P = 0.162$

*Values are given as mean (SD)

†Values are given as median (interquartile interval).

‡$P \leq 0.05$ (2-tailed).

AC indicates Abdominal circumference; Hb, hemoglobin concentration; Ht, hematocrit; WBC, white blood cell count; NC, neutrophil count; PC, platelet count; MDA, malonaldehyde.

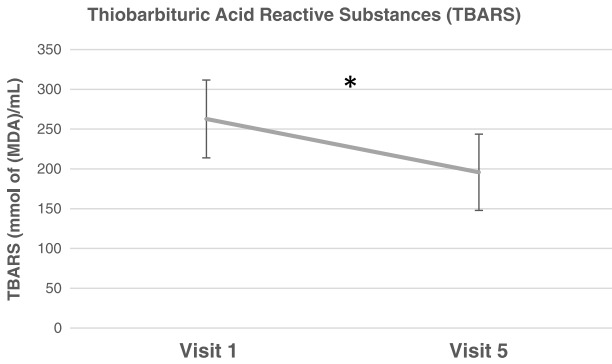

FIGURE 3. Thiobarbituric acid reactive substances at visits 1 and 5. Error bars indicate ±1 SD; *$P = 0.002$ (paired-sample t test).

was accompanied by a reduction in folic acid serum levels. Patients' folate may have been used to restore ALA and ensure its antioxidant activity. Future studies will elucidate if folate supplementation is necessary for long-term ALA treatment.

AUTHOR DISCLOSURE INFORMATION

The Conselho Nacional de Desenvolvimento Científico e Tecnológico (Brazil) funded this study.

The authors declare no conflict of interest.

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